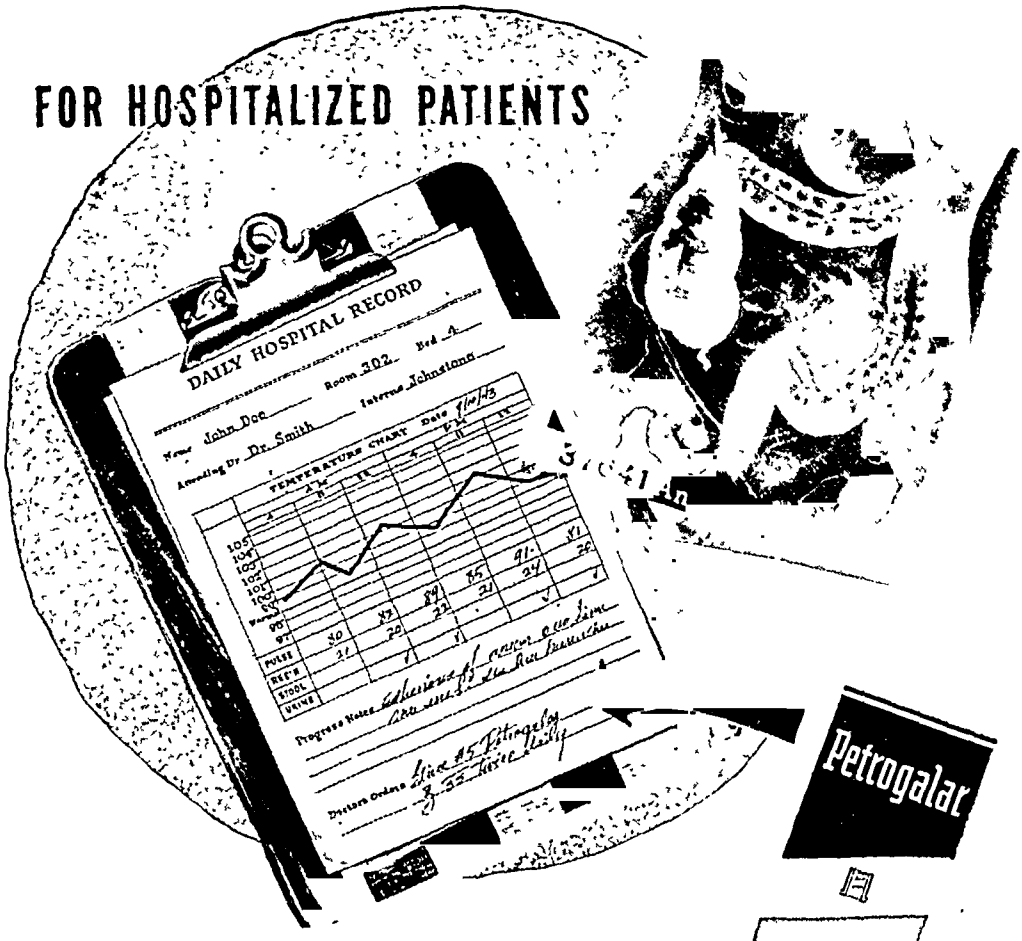
FOR HOSPITALIZED PATIENTS



for the management of constipation

Petrogalar is an aid to the comfort of hospitalized patients. Those receiving Petrogalar require less individual attention and fewer visits from busy internes and nurses. Petrogalar relieves nurses of the extra burden of having to change bed linens and sleeping garments as a result of "leakage" sometimes caused by plain mineral oil.

The special 10⅔ ounce Petrogalar Hospital Dispensing Unit allows the physician complete control over the administration of a routine laxative during confinement.

Years of professional use have established Petrogalar as a reliable, efficacious aid for the restoration and maintenance of comfortable bowel action.

PETROGALAR LABORATORIES, INC., CHICAGO, ILL.

Copyright 1943, by Petrogalar Laboratories, Inc.

DIVISION *Wyeth* INCORPORATED

Petrogalar is an aqueous suspension of pure mineral oil each 100 cc. of which contains 65 cc. pure mineral oil suspended in an aqueous jelly.

Petrogalar

REG. U.S. PAT. OFF.

Constant uniformity assures palatability —normal fecal consistency. Five types of Petrogalar provide convenient variability for individual needs.

Entered as second-class matter February 3, 1943, at the post office at Baltimore, Maryland, under the Act of March 2, 1879. Subscription price, $3.00 per volume. Single numbers 50 cents.

In gastric and duodenal ulcer...

PABLUM

as a palatable cereal food of high nutritional value has the following advantages: (1) rich in iron and calcium; (2) a good source of the vitamin B complex; (3) low fiber content and (4) convenience.

Pablum is convenient because it requires no cooking. Thus, the patient can prepare his meal at the office or shop simply by adding milk at any temperature. Pablum absorbs about 12 times its own weight of milk, so that it offers a good vehicle for milk.

In ulcerative colitis and intestinal tuberculosis, Pablum has also been found useful in the dietary.

Composition of Pablum

Wheatmeal (farina)	52%
Oatmeal	18
Wheat Germ	15
Cornmeal	10
Powdered Beef Bone (Specially prepared for human use)	2
Sodium chloride	1
Alfalfa Leaf	1
Dried Brewers Yeast	1
Reduced iron (11 Gm. per 100 lbs.)	

Approximate Analysis of Pablum

Carbohydrate (by difference)	69.9%
Protein (N X 6.25)	15.0
Moisture	7.0
Minerals (ash)*	4.2
Fat (ether extract)	3.0
Crude Fiber	0.9
*Including:	
Calcium	0.78%
Phosphorus	0.62
Iron	0.03
Copper	0.0013

Approximately 106 Calories per oz. or 3.7 per Gm. 12 level tablespoonfuls = 1 oz.
Each ounce contains not less than 0.3 mg. thiamine (vitamin B_1) and 0.1 mg. riboflavin (vitamin G).

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U.S.A.

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

(In writing to advertisers, please mention the journal—it helps.)

in the Medical Management of BILIARY TRACT DISEASE

The administration of Decholin, the original dehydrocholic (triketocholanic) acid, either orally or intravenously in the form of Decholin sodium, is followed by an increase in secretion of bile which may amount to as much as 200 per cent.

This thin, free-flowing liver-bile, secreted under considerably greater pressure, serves the valuable purpose of flushing both, the intrahepatic as well as the extrahepatic passages. Mucus, inspissated bile, gravel, and pus-laden secretions (if present) are washed before it.

This therapeutic influence is used to advantage in the medical management of many biliary tract disorders. It is the keystone of therapy in chronic cholecystitis, noncalculous cholangitis, biliary engorgement, biliary dyskinesia, hepatic insufficiency. It produces not only symptomatic relief, but demonstrable, objective improvement. Combined with a diet high in fat, it promotes drainage of the entire biliary tree, including the gallbladder. • Decholin is contraindicated in complete obstruction of the common or hepatic bile duct.

Physicians are invited to send for a copy of the 4th (condensed) edition of the brochure "Biliary Tract Disturbances"

Riedel - de Haen, Inc. • New York 13, N. Y.

COUNCIL ACCEPTED SINCE 1932

Decholin

REG. U.S. PAT. OFF.

PACE-MAKER OF BILE ACID THERAPY

VOLUME 2, NUMBER 1 JANUARY, 1944

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

TABLE OF CONTENTS

EDITORIALS

BOOK REVIEWS

THE VALUE of Aluminum Hydroxide Gel in the treatment of gastric and duodenal ulcers is well established. However, two questions arise in the minds of patients: length of treatment—and taste.

Since Aluminum Hydroxide Gel is generally administered at from two- to four-hour intervals, with therapy extending over a period of several months, taste becomes an important consideration. Therefore, when the Squibb Laboratories decided to produce Aluminum Hydroxide Gel, particular attention was paid to taste.

It's non-irritating and non-toxic. In addition, the fluidity has been carefully adjusted to permit easy pouring—and the flavoring doesn't tire the taste.

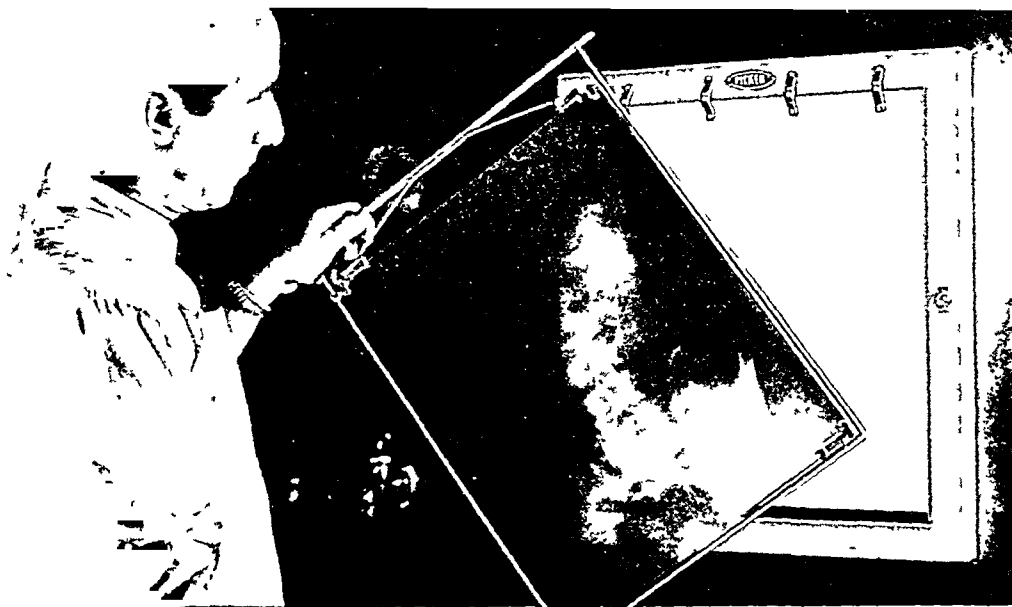
For these reasons we would like you to try Squibb Aluminum Hydroxide Gel. Compared with whatever standards you select, you will find it worth prescribing regularly. It is supplied in 12-oz. bottles.

For literature address the Professional Service Dept., 745 Fifth Avenue, New York 22, N. Y.

E·R·SQUIBB & SONS

Manufacturing Chemists to the Medical Profession Since 1858

better in 6 ways



In a series of comparative tests made under rigid laboratory control, using aluminum wedge exposures, with all density and control curves determined by densitometric measurements, these Picker concentrated processing solutions have demonstrated clear superiority over leading competitive brands on every point.

Clearmix Medical X-Ray Developer and Perfix Medical X-Ray Fixer will produce . . . *in your own darkroom* . . . the most satisfactory results possible in terms of speed, clarity, contrast and detail. Send for our bulletin giving details of tests, time-temperature charts, and prices.

1. **miscibility**
2. **processing speed**
3. **contrast and detail**
4. **hardening**
5. **slow exhaustion**
6. **non-fogging**

***Medical* X-Ray Developer**

***Medical* X-Ray Fixer**

PICKER X-RAY
CORPORATION
300 FOURTH AVE • NEW YORK 10, N. Y.

VOLUME 11, NUMBER 1

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

WALTER C. ALVAREZ, *Editor*

A. C. IVY, *Assistant Editor*

ASSOCIATE EDITORS AND THEIR SUBJECTS

A. H. Aaron, *Technical Matters*
J. A. Bargen, *Large Intestine*
H. L. Bockus, *Liver and Gall Bladder*
W. C. Boeck, *Parasitology*
B. B. Crohn, *Small Intestine*
Robert Elman, *Pancreas*
Franklin Hollander, *Abstracts**
Sara M. Jordan, *Stomach*
J. L. Kantor, *Military Gastroenterology*
B. R. Kirklin, *Radiology*
Paul Klemperer, *Pathology*
F. H. Lahey, *Surgery*
F. C. Mann, *Physiology*
H. J. Moersch, *Esophagus*
V. C. Myers, *Biochemistry*
W. L. Palmer, *Stomach*
J. M. Ruffin, *General Reference*
Rudolf Schindler, *Gastroscopy*
D. L. Wilbur, *Nutrition*

*Assisted by a staff of 30 abstractors

EDITORIAL COUNCIL

IRVIN ABELL
A. F. R. ANDRESEN
LLOYD ARNOLD
B. P. BABKIN
C. J. BARBORKA
W. A. BASTEDO
E. B. BENEDICT
A. A. BERG
J. M. BLACKFORD
LEON BLOCK
R. S. BOLES
J. L. BORELAND
R. C. BROWN
T. R. BROWN
J. T. CASE
L. G. COLE
E. N. COLLINS
G. R. COWGILL
C. W. DOWDEN
L. R. DRAGSTEDT
E. S. EMERY, JR.
G. B. EUSTERMAN
J. H. FITZGIBBON
E. B. FREEMAN
E. H. GAITHER
L. C. GATEWOOD
F. D. GORHAM
R. H. M. HARDISTY
SEALE HARRIS
C. G. HEYD
A. A. JONES
C. M. JONES
C. R. JONES
N. W. JONES
J. W. LARIMORE
J. M. LYNCH
B. B. V. LYON
T. T. MACKIE
LAY MARTIN
J. G. MATEER
T. G. MILLER
W. G. MORGAN
H. NECHELES
MOSES PAULSON
G. M. PIERSOL
J. T. PILCHER
M. M. PORTIS
J. P. QUIGLEY
MARTIN REHFUSS
V. C. ROWLAND
ADOLPH SACHS
LEON SCHIFF
H. F. SHATTUCK
D. N. SILVERMAN
V. E. SIMPSON
A. M. SNELL
W. H. STEWART
H. M. SOPER
J. E. THOMAS
E. J. VAN LIERE
M. G. VORHAUS
F. W. WHITE

Published by

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, MD.

(In writing to advertisers, please mention the journal—it helps.)

I WANT TO GROW

WITH

CEREVIM

Lederle

GROWTH MEANS FOOD—in fact, growth *is* food in living, transmuted form.

CEREVIM is an excellent source of nourishment furnishing proteins, carbohydrates and fats essential to normal growth (108 calories per ounce.) It was the first infant cereal food to provide in a single 1 ounce serving, the complete recommended daily allowances of vitamins and minerals.

	Thiamine	*Riboflavin*	*Niacin*	*Iron*	*Calcium*
1 oz.	0.6 mg.	0.9 mg.	6.0 mg.	7.5 mg.	220 mg.
2 oz.	1.2 mg.	1.8 mg.	12.0 mg.	15.0 mg.	440 mg.
3 oz.	1.8 mg.	2.7 mg.	18.0 mg.	22.5 mg.	660 mg.

The percentages of essential amino acids in CEREVIM closely parallel the percentages considered essential in the daily diet.

Cerevim Is Unrationed!

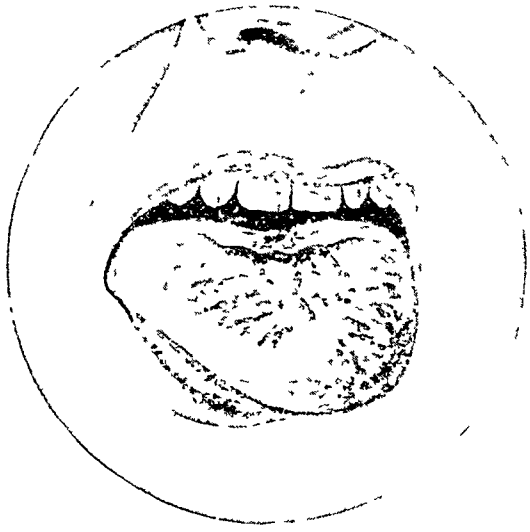
Moisture-resistant, wax-sealed package with handy pouring spout.

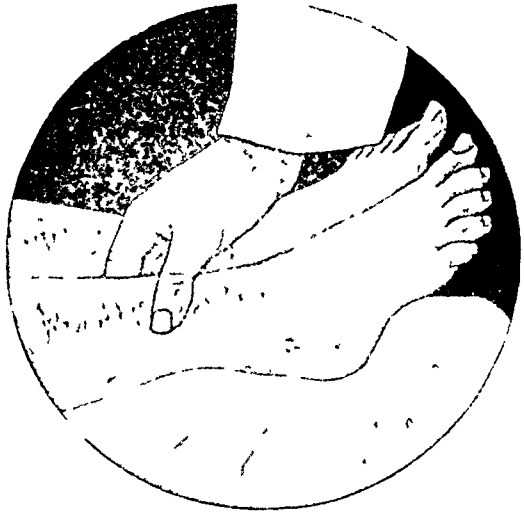
PACKAGES—½ and 1 pound

LEDERLE LABORATORIES INC.

30 ROCKEFELLER PLAZA, NEW YORK 20 NEW YORK

(In writing to advertisers, please mention the journal—it helps.)





BEFORE THE TEXTBOOK PICTURE DEVELOPS

Today the physician seldom sees a typical textbook case of fully developed B Complex deficiency.

On the other hand, there are thousands of patients who are partially lacking in these essential vitamin factors—patients in whom optimum improvement is noted only when replacement therapy with *Whole Natural* Vitamin B Complex is instituted.

The clinical demand for an easily administered source of *Whole Natural* Vitamin B Complex in concentrated form furnished the spark for research which led to the development of **BEZON.**

BEZON* is *Whole Natural* Vitamin B Complex—concentrated to high potency from natural sources—no synthetic vitamin factors are added.

★ *Whole* B Complex is important because B deficiencies in man are almost always multiple—a diet poor in one factor of the B Complex is apt to be lacking in other factors.

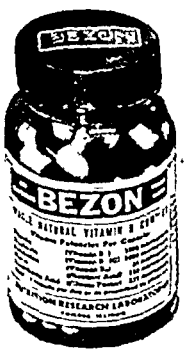
★ *Natural* B Complex is important because only in *Whole Natural* Vitamin B Complex can *all* 22 vitamin B factors be obtained.

BEZON is made only in the distinctive two-color gelatin capsule. Supplied in bottles of 30 and 100 capsules.

Samples and literature available on request

NUTRITION RESEARCH LABORATORIES • CHICAGO

*Trade Mark



BEZON

WHOLE NATURAL *VITAMIN B COMPLEX*

ETHICALLY PROMOTED—MADE BY THE MAKERS OF ERTRON

He'll get his Carnation ... in '44

This is the picture of Carnation *availability,* as we see it for 1944.

Naturally, the Carnation Company is being called on to supply large amounts of milk for our armed forces, and for our government's Lend-Lease program.

But adequate amounts will also be available for essential civilian needs, foremost among which are infant feeding and the special diet requirements of older persons.

Under rationing, there should be *ample* stocks of Irradiated Carnation Evaporated Milk for these purposes, in the hands of grocers in all sections of the country.

And you may be certain that the Carnation Company will cooperate to the full, as in the past, to make sure that every baby on a Carnation formula can *continue* on it.

We believe that physicians, and mothers, will feel that the high quality of Irradiated Carnation Milk will more than justify *specifying* it—and, should it be necessary, going to a little trouble to get it.

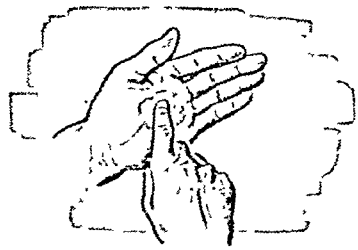
CARNATION COMPANY, MILWAUKEE, WIS.

IRRADIATED

Carnation 

Milk

"FROM CONTENTED COWS"



Non-Irritating Bulk

—non-digestible and non-absorptive of vitamins—makes this hydrophilic colloid a favored laxative in colitis

Mucilose

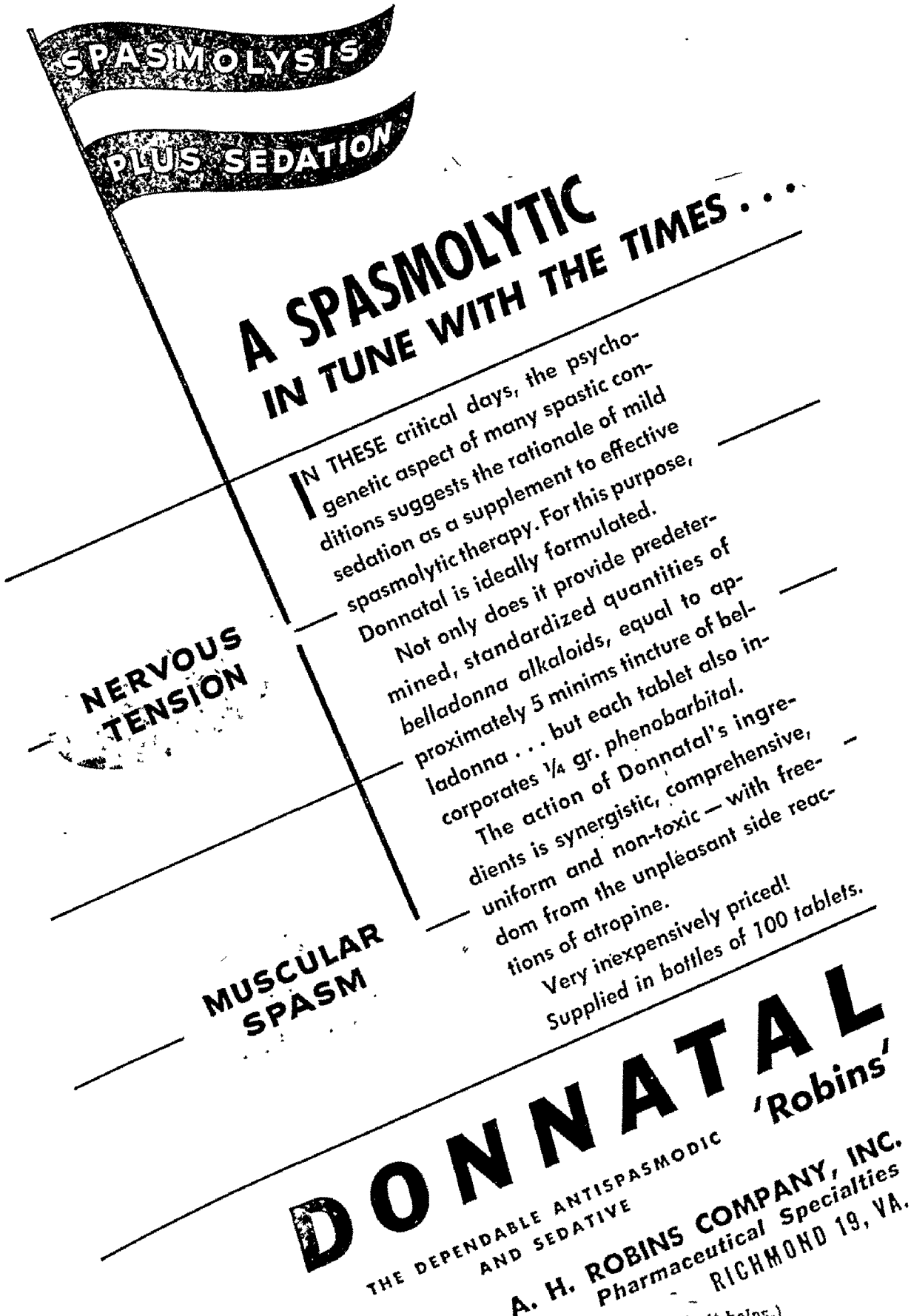
This highly purified hemicellulose is available in 4-oz. and 16-oz. bottles as Mucilose Flakes and Mucilose Granules.

Frederick Stearns & Company

Since 1855 . . . ESSENTIALS OF THE PHYSICIAN'S ARMAMENTARIUM

NEW YORK KANSAS CITY DETROIT, MICH. SAN FRANCISCO WINDSOR, ONTARIO
SYDNEY, AUSTRALIA AUCKLAND, NEW ZEALAND

(In writing to advertisers, please mention the journal—it helps.)



(In writing to advertisers, please mention the journal—it helps.)

better than a "Get Well" card

• For convalescents, malnourished children and adults or geriatric patients who may not derive full benefit from vitamin therapy unless accompanied by measures to improve digestion, TAKA-COMBEX* Kapseals* are more and more prescribed by many physicians.

Addition of Taka-Diastase to a potent B-complex formula makes TAKA-COMBEX Kapseals especially useful when processes of digestion and absorption do not proceed in a normal manner.

TAKA-COMBEX Kapseals are indicated in anorexia, polyneuritis, pregnancy, lactation, cardiac decompensation, hypothyroidism, febrile illnesses, convalescence and restricted diet when associated with deficiency of B vitamins or faulty digestion of starches.

Each TAKA-COMBEX Kapseal contains:

Taka-Diastase	2.5 Grains	Vitamin B_6	0.5 mg.
Vitamin B_1	3 mg.	Pantothenic acid	3 mg.
Vitamin B_2	3 mg.	Nicotinic acid	10 mg.

With other components of the vitamin B-complex as derived from liver.

PARKE, DAVIS & COMPANY

DETROIT, MICHIGAN

(In writing to advertisers, please mention the journal—it helps.)

"HERE YOU WERE...10 DAYS AGO!"

It's mighty satisfying to see, as you often can, complete disappearance of the peptic ulcer niche, after a 10-day ulcer regime with Amphojel.† In addition to promoting rapid healing of ulcer, Amphojel offers:

Prompt relief from pain . . .
Fewer recurrences . . .
Superior weight gain during treatment . . .
No alkalosis.

Available in 12 fluid ounce bottles. A pharmaceutical of John Wyeth & Brother, Division WYETH Incorporated, Philadelphia.

AMPHOJEL*'
Wyeth's
ALUMINA GEL
REG U.S PAT OFF.

†W OLDMAN, E. E. and POLAN, C. G.: The Value of Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer; A review of 407 Consecutive Cases, Am J. M. Sc. *198* 155-164 (Aug) 1939.

(In writing to advertisers, please mention the journal—it helps.)

ADDISONIAN PERNICIOUS ANEMIA WITHOUT ACHLORHYDRIA: DOES IT EXIST?[1]

JOHN MARTIN ASKEY, M.D.
Los Angeles, California

THE PROBLEM

Can Addisonian pernicious anemia occur in the presence of gastric secretion of free hydrochloric acid? This is entirely contrary to the natural history of the typical disease.

Cornell said in 1927, "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this, the stomach contents do not contain free hydrochloric acid" (1). Many reports of "pernicious anemia without achlorhydria" have appeared, however, and such a diagnostic paradox apparently has been accepted (2–29).

Such a diagnosis should not be accepted unless based upon precise data. This poses the question, what are the precise diagnostic criteria of Addisonian pernicious anemia? It is a diagnosis easy to make, but hard to prove. The ordinary diagnosis is a presumptive diagnosis. The essential findings of Addisonian pernicious anemia are a primary loss of Castle's gastric intrinsic factor inducing a secondary loss of a specific liver principle or principles, the critical reduction of which produces the characteristic blood, bone marrow, and nerve tissue changes. The characteristic mechanism involved in producing this critical liver depletion is the idiopathic loss of gastric factor. These losses are assumed, but not proved in the ordinary diagnosis.

Macrocytic hyperchromic anemia, glossitis, sub-acute combined cord degeneration and anacidity in a Caucasian in the temperate zone, with clinical and hematologic improvement following liver administration are presumptively due to Addisonian pernicious anemia. That is, it is assumed that an idiopathic loss of intrinsic factor has occurred, causing the critical liver depletion. These losses are not proved, but for all practical purposes these presumptive data are sufficient. The ordinary objective findings, so compositely characteristic of Addisonian pernicious anemia, still are neither precise nor specific. They can occur in other conditions (Table I) (31–34). When ordinary objective and subjective findings, however, are so typical, there is no reason to require precise data. But when the most constant objective finding, anacidity, is lacking, precise diagnostic data are mandatory. The diagnosis must be proved.

[1] From the Department of Medicine, University of Southern California School of Medicine.

THE CRITERIA FOR A PRECISE DIAGNOSIS

How can the diagnosis be incontrovertibly established? Demonstration of loss of gastric intrinsic factor alone is not enough to prove the existence of Addisonian pernicious anemia. Intrinsic factor may be lost in a number of other conditions (Table II) (35–41). The idiopathic nature of the loss of gastric intrinsic factor is the pathognomonic feature, not the loss per se. Gastric intrinsic factor is lost in every patient with Addisonian pernicious

TABLE I

Objective findings in Addisonian pernicious anemia

1. Anacidity 2. Macrocytic hyperchromic anemia 3. Subacute combined degeneration of the spinal cord 4. Glossitis	Common objective findings amenable to ordinary clinical examination. Non-specific, however. May occur in other disorders (31–34)
5. Reduction of intrinsic factor 6. Loss of specific liver principle	If proved to be idiopathic, these are composite specific objective findings. Loss of intrinsic factor is possible but impracticable to demonstrate. Loss of specific liver principle can be tested for only directly if patient dies. Indirect test is by determining response to liver. Not precise because liver extract contains several antimacrocytic anemia factions

TABLE II

Macrocytic anemia due to loss of intrinsic factor

1. Idiopathic loss—Addisonian pernicious anemia
2. Loss secondary to
   - A. Gastric neoplasm (35, 36)
   - B. Pregnancy (41)
   - C. Sprue (37)
   - D. Avitaminosis
   - E. Intestinal strictures and anastomoses (38, 39, 40)
   - F. Gastrectomy (total)

anemia, but every individual with loss of gastric intrinsic factor does not have Addisonian pernicious anemia. What characterizes the loss of intrinsic factor in Addisonian pernicious anemia? The natural history of the disease indicates that it occurs insidiously, paralleled by an insidious loss of the specific liver principle; both are ordinarily preceded by many years of anacidity. The triad-histamine anacidity, reduction of intrinsic factor and reduction of the specific liver principle are essential objective changes of typical Addisonian pernicious anemia.

Addisonian pernicious anemia paradoxically can occur with little or no anemia (30), and little or no nerve tissue changes, but even in such cases the above triad will obtain. To establish the diagnosis where anacidity is absent, it is necessary that the other essential objective changes in the triad be proved. A precise diagnosis demands that the reduction of gastric intrinsic factor and reduction of the specific liver principle be proved. To be significant, the loss of intrinsic factor must be shown to be idiopathic by exclusion of the other conditions that may induce it. Pregnancy, gastric neoplasm, sprue, intestinal strictures and ulcers and avitaminosis (35, 36, 37, 38, 39, 40, 41) have been shown at times to be associated with loss of intrinsic factor and macrocytic anemia. The mechanism of the loss of intrinsic factor in these conditions is not the same as in Addisonian pernicious anemia.

It is impractical to demonstrate reduction in both intrinsic factor and in the specific liver principle. The impracticality, however, in no way lessens the necessity for demonstration if a precise diagnosis is to be made. Direct studies by a biologic assay of the liver can be made only if the patient dies; indirect data obtained by the response of the patient to administration of the liver extract ordinarily used unfortunately are not precise. The liver extract usually used is Cohn's Fraction G (44) which contains not only the specific anti-pernicious anemia principles, but also different fractions which have been shown to be effective in the nutritional macrocytic anemias of the tropics, but not against Addisonian pernicious anemia (43). It is impossible to know, therefore, whether improvement of a macrocytic anemia following administration of Cohn's fraction G is due to the specific anti-pernicious anemia fraction or to the fraction effective against nutritional macrocytic anemia. Before a macrocytic anemia, associated with presence of free hydrochloric acid can be logically called Addisonian pernicious anemia, one must apply the following catechism:

1. Were all other possible causes of macrocytic anemia excluded?
2. Was the absence of intrinsic factor established by biologic assay?
3. Was the anemia shown to be due to deficiency of the specific anti-pernicious anemia liver principle?

The presence of cirrhosis of the liver, extreme hypothyroidism, pregnancy, sprue, pellagra, gastric neoplasm, intestinal strictures and anastomoses or gross nutritional deficiencies, are adequate causes for a macrocytic anemia, and preclude the diagnosis of true pernicious anemia.

If any of these conditions exist, the diagnosis cannot be Addisonian pernicious anemia unless the two diseases coexist. Some are easily excluded. Pregnancy, sprue, and pellagra ordinarily will be obvious. Gastric neoplasm can ordinarily be shown easily by roentgenograms. Liver function tests should be employed as an aid to the recognition of cirrhosis of the liver.

The exclusion of dietary deficiency and of small intestinal lesions is more difficult. Dietary deficiency is unessential for the development of Addisonian pernicious anemia. If prolonged under-nutrition has been present in a patient with macrocytic anemia and retention of free acid, Addisonian pernicious anemia is not the logical diagnosis. The logical diagnosis is nutritional macrocytic anemia. Furthermore, unless a case report of pernicious anemia without achlorhydria stipulates that under-nutrition has been ruled out, the report is unacceptable.

Exclusion of small bowel lesions is essential. A special roentgenologic study is necessary and unless such a careful study has been made, a diagnosis of pernicious anemia without achlorhydria is untenable. The presence of stenoses and strictures excludes Addisonian pernicious anemia and the presence of other lesions such as diverticula, throws justifiable doubt on the diagnosis. It cannot be proved they do not impair intestinal absorption and thus produce the macrocytic anemia by a mechanism different than that of Addisonian pernicious anemia.

A favorable response to liver therapy with Cohn's fraction G is no specific diagnostic differentiation. The macrocytic anemias of sprue, pellagra, intestinal strictures and nutritional macrocytic anemia may all respond to such liver administration. The Dakin-West fraction (45) separated from the original Cohn fraction G has been shown to be effective against pernicious anemia and ineffective against tropical nutritional macrocytic anemia. Enough data are not available to state whether it is ineffective against all other nutritional macrocytic anemias. If the response to liver is to be used as a therapeutic test, however, a favorable response is of little significance unless the Dakin-West fraction or one of the other highly purified fractions obtained from the original Cohn's fraction G is used.

The response to desiccated hog stomach or ventriculin should be a more precise therapeutic test. It presumably supplies only intrinsic and extrinsic factors, and should correct no other deficiency than that of the anti-pernicious anemia liver principles.

The precise diagnosis of Addisonian pernicious anemia, therefore, requires: 1. Elimination of the conditions other than Addisonian pernicious anemia which may cause a loss of intrinsic factor. 2. A biologic assay showing absence of intrinsic factor. 3. A response to desiccated hog stomach which furnishes ultimately the specific anti-pernicious anemia liver principle, or to a highly purified liver fraction, such as the Dakin-West fraction.

These postulates, although rigid, are mandatory if pernicious anemia is to be diagnosed in an individual with acid present. The diagnosis, not infrequently has been made, and later, proved to be wrong. Hurst (46a, b) reports two such cases. Weber and Huber report a patient with a blood picture typical

of pernicious anemia who responded to liver treatment but showed a perforating jejunal ulcer at necropsy (47).

REVIEW OF REPORTED CASES

Forty-seven reports in the literature of cases of pernicious anemia without achlorhydria have been reviewed.

Many can be excluded because of too few details (Table III). In others, there are data which suggest another cause for the anemia. In fifteen cases clinical data were sufficiently characteristic to accept them as possible cases, but complete precise criteria were not established (Table IV). In one instance, Beebe and Wintrobe (14) demonstrated a lack of intrinsic factor by the biologic assay. No gastrointestinal X-ray study was done, however, and liver depletion of the specific anti-pernicious anemia principle was not proved.

In six of these fifteen cases, no gastrointestinal X-ray examinations were made. Four cases are accepted because necropsies revealed no obvious organic cause for the anemia. Five of these cases were reported before the discovery of liver therapy. They are acceptable but not convincing.

Hartfall's case (6) showed no abnormal findings by gastrointestinal X-ray. There was a typical reticulocyte and erythrocyte response. The spleen was enlarged two inches below the costal margin. No liver function test save the van den Bergh test was done. Splenomegaly is no contradiction to the diagnosis of Addisonian pernicious anemia, but it is uncommon enough that if it occurs in a questionable case of pernicious anemia, such as in a patient who has retained hydrochloric acid secretion, that it must be proved that the splenomegaly is not due to liver disease. In such cases, the diagnosis of Addisonian pernicious anemia cannot be accepted unless liver function tests have been utilized.

Wilkinson's (8) two cases were quite typical in their response to ventriculin. The gastrointestinal X-ray studies showed no lesions, and in one patient a biologic assay revealed no intrinsic factor. Both patients, however, had splenomegaly and had had recent jaundice. No data were given as to prolonged undernutrition and no liver function tests were made to furnish data as to possible cirrhosis of the liver.

Harvey and Murphy's (13) patient had typical blood and neurological findings. Other findings were atypical, however. Multiple diverticula were found in the small intestines; the blood response was poor, the patient died despite liver treatment, and at necropsy, liver damage was demonstrated. No precise findings were established.

Thirty-two other cases in the literature have been rejected because other causes for the anemia were present or the data were unconvincing.

TABLE III

Reported cases of pernicious anemia without achlorhydria

(Cases not acceptable)

REPORTED BY	NO. OF CASES	REMARKS
Bloch (1903)	1	Insufficient details (pre-liver)
Weber (1909)	2	First, adenopathy, bleeding gums, retinal hemorrhage. Second, syphilitic (pre-liver)
Passey (1922)	1	Insufficient details (pre-liver)
Willebrand (1922)	1	Anemia became hypochromic and a ten-year remission occurred (pre-liver)
Shackle (1923)	1	Considered a "septic anemia" by Hurst
Heath (1928)	2	First, no response to liver. Second, questionable pellagra
Loewenberg and Gottheil (1928)	1	Insufficient details
Levine and Ladd (1921)	2	Two cases unacceptable. One, anemia followed intestinal resection; the other, possible spinal cord tumor
Grinker (1926)	3	Insufficient details
Wilkinson (1932)	4	Four cases unacceptable. One (Case VI), malignancy of throat. Second (Case IV), not typical. Third (Case V), not typical. No gastro-intestinal x-ray. No dietary data. No liver function tests. Fourth (Case VIII) not typical. Blood response poor. No dietary data. Van den Bergh's test negative. No other liver function tests
Seyderhelm and Opitz (1928)	1	Cites no details
Nielsen (1941)	2	Diet in both cases bad. No gastro-intestinal x-rays. One did not respond to liver
Levin (1934)	1	Liver and spleen enlarged. Icterus index 32. Negative gastro-intestinal x-ray. No dietary data. No liver function tests
Davidson (1933)	1	Repeated malaria. Large liver and spleen. Marked dietary defect
Castle, Heath and Strauss (1931)	2	Blood typical, biologic assays showed no intrinsic factor. But one had sprue. The other multiple intestinal anastomoses
Alsted (1934)	2	First, possible tuberculous enteritis or sprue. Second, insufficient data. No gastro-intestinal x-ray
Faber and Gram (1924)	2	Two cases unacceptable. One had hemorrhagic disease and the other had marked thrombocytopenia
G. T. O'Brien (1933)	1	Insufficient data
Hurst (1930)	1	No gastro-intestinal x-ray. Splenomegaly. Positive indirect van den Bergh test. No other liver function test. No dietary data
Hurst (1932)	1	Patient alcoholic. Anemia improved without liver therapy after alcohol stopped and infected teeth removed
Total	32	

TABLE IV

Reported cases of pernicious anemia without achlorhydria

(Possible cases but not proved)

REPORTED BY	NO. OF CASES	REMARKS
Shaw (1926)	1	Remission with transfusions. Palpable spleen (pre-liver)
Ungley (1929)	1	One case of two. Age 26, increased cell fragility, but necropsy showed "pernicious anemia". Based on necropsy
Levine and Ladd (1921)	1	(Pre-liver) necropsy—"pernicious anemia". Based on necropsy. Other data unconvincing
Faber and Gram (1924)	2	(Pre-liver) necropsy in one. "Anemia". Based on necropsy
Hartfall (1933)	1	Negative gastro-intestinal x-ray. Responded to liver, direct van den Bergh negative. Splenomegaly. No dietary data. No other liver function tests. No precise data.
Moore and O'Farrell (1933)	1	Responded to liver. No gastro-intestinal x-ray mentioned. No data as to dietary lack. No liver function test. No precise data
Wilkinson (1932)	2	Cases III and VII. Both splenomegaly and recent jaundice. Both responded to ventriculin. Biologic assay showed no intrinsic factor in one (case VII); "van den Bergh reaction positive delayed", (Case VII); "Positive indirect", (Case III). No other liver function tests. No dietary data. Gastro-intestinal x-ray negative
McPeak and Neighbor (1927)	1	No gastro-intestinal x-ray. Typical liver response. No precise data
Connery and Jolliffe (56) (1931)	1	Typical clinical picture. Typical reticulocyte response to liver. Negative gastro-intestinal x-ray. No increase in urinary urobilinogen. Direct van den Bergh negative. Indirect van den Bergh positive. No dietary data save "distaste for meat". No precise data
Finney (1939)	1	Red blood cell response to liver slow. No gastro-intestinal x-ray. Marked neurologic involvement. Van den Bergh test negative. No other liver function tests. No dietary data. No precise data
Harvey and Murphy (1933)	2	Typical blood and neurological findings. Multiple diverticula of small bowel. Subnormal reticulocyte and red blood cell response. Became progressively worse and died despite liver treatment. A/G ratio normal. Necropsy, gall bladder disease with liver damage. No precise data
Beebe and Wintrobe (1933)	1	No intrinsic factor by biologic assay. No gastro-intestinal x-ray. No liver function tests. No dietary data
Total	15	

Very few of the patients have been studied with respect to a long standing avitaminosis. It must be shown that dietary under-nutrition has not existed, for typical Addisonian pernicious anemia can occur in people with a normal diet. There are a number of these cases which fulfilled all the ordinary presumptive criteria for the diagnosis of Addisonian pernicious anemia. The fact remains that none of them has been proved by complete precise criteria to be Addisonian pernicious anemia. It has never been established beyond doubt that Addisonian pernicious anemia can exist with persistence of secretion of hydrochloric acid. The diagnosis of Addisonian pernicious anemia without achlorhydria has been a presumption, not an established verity.

As long as the term "pernicious anemia" is applied uncritically to various macrocytic anemias, confusion will continue. "Pernicious anemia of pregnancy", "pernicious anemia of pellagra", "pernicious anemia of sprue", are all terms continuing to obfuscate the clinical picture.

DISCUSSION

Although anacidity is constant in Addisonian pernicious anemia, yet anacidity bears no essential role in the pathogenesis of the disease. The essential disturbance is in the intrinsic factor-extrinsic factor interaction. The precise relationship of the secretion of acid to the secretion of intrinsic factor in Addisonian pernicious anemia is unknown. Until this relationship is known, it is impossible to say whether or not Addisonian pernicious anemia without achlorhydria can exist.

The diagnosis implies loss of ability to secrete intrinsic factor and retention of secretion of hydrochloric acid. Hydrochloric acid is secreted in the parietal fundic cells. The actual cells that secrete intrinsic factor are as yet unidentified. In the stomach the site of secretion has been localized to the fundus glands (48), but whether the stomach is the sole site of intrinsic factor secretion has not been proved.

The only direct studies in the human have been on the stomach and duodenum. No direct studies have been made to determine its presence in the human intestine. Tests on animals have been more extensive (49–50), but apply only to those particular animals studied and should be applied by analogy to the human only with great caution. If one point has been established in the last few years it is this, that Addisonian pernicious anemia is a disease occurring essentially in humans and only data obtained from investigations of the human are of critical value. Animal experimentation can suggest inferences, but such inferences must be confirmed or disproved by investigations on the human.

The demonstration of anti-anemic potency of swine's large and small intestine mucosa, therefore, is chiefly of value in projecting the question, is

this true of human intestinal mucosa? Even the demonstration of anti-anemic potency of the intestine is not accepted as proof of intrinsic factor secretion, since it has not been agreed whether the anti-anemic potency in the hog is due to secretion of intrinsic factor in the intestinal mucosa or to mere adsorption of the liver principle already formed from interaction of the stomach and food factors (51). No feeding experiments have been made with hog intestine following total gastrectomy. Such experiments might indicate whether the anti-anemic potency was due to secretion of intrinsic factor or the adsorption of liver substance.

Jacobson (52) observed loss of argentaffine cells in the stomach and intestine of patients dying of pernicious anemia, and tentatively inferred that they might be the cells producing intrinsic factor, and that intrinsic factor secretion occurred in the normal human intestine. Of this we have no proof. If intrinsic factor is secreted solely in the fundus glands of the stomach, the diagnosis of Addisonian pernicious anemia without achlorhydria implies an unusual functional secretory dissociation of the fundus glands, whereby they lose the ability to secrete intrinsic factor but retain the ability to secrete hydrochloric acid. Until the exact site of intrinsic factor secretion is determined, the exact relationship of secretion of hydrochloric acid cannot be known.

The chronology of events in typical Addisonian pernicious anemia as given by Castle is generally accepted. In relapse, severe atrophic gastritis of the fundus with disappearance of the specific glandular elements occurs, accounting apparently for the reduction of intrinsic factor. Loss of anti-pernicious anemia liver substance then occurs, producing blood, bone marrow and nerve changes. The failure of partial gastric resections to produce pernicious anemia is thus logically ascribed to the preservation of the cardia, which is an active site of secretion of intrinsic factor. This reasoning does not apply readily to all humans.

If the reduction of intrinsic factor (it is not a complete loss) can produce Addisonian pernicious anemia, why does not the complete anatomical extirpation of that gastric intrinsic factor always do it? A number of patients have lived two to four years following total gastrectomy without developing pernicious anemia. Allen (53) reported one patient alive and well with a normal blood picture four and one-half years after total gastrectomy. This has not been adequately explained. Such failure to develop pernicious anemia has been explained as due to either possession by the patient of sufficient anti-pernicious anemia material to last years, or to a continuing production of anti-pernicious anemia material due to extra gastric source of intrinsic factor.

Such explanations hinge, therefore, upon the assumption that there continues to be a supply of anti-pernicious anemia liver material despite total

gastrectomy. This is another assumption, not a deduction from facts. Unfortunately, we have no knowledge of what happens to the supply of human anti-pernicious anemia liver principle after total gastrectomy. Anatomical removal of the source of gastric intrinsic factor either does or does not exhaust the human liver of anti-pernicious anemia material, but direct studies on the human to determine what happens have not been made. We have only the results of total gastrectomy in animals.

Total gastrectomy in the hog produces exhaustion of the supply of anti-pernicious anemia principle in the liver (54–55). No such tests of the human liver several years after total gastrectomy have been made. If the sole source of intrinsic factor is the stomach, the liver should gradually be depleted and pernicious anemia result as soon as the depletion reaches a critical level. Complete exhaustion of the liver of anti-pernicious anemia material following total gastrectomy in the swine occurs after six months (55). Bussabarger and Ivy (42) found that total gastrectomy of monkeys did not produce pernicious anemia. They concluded that "Since gastrectomy did not produce pernicious anemia, either the stomach is not the sole source of intrinsic factor, or the simple loss of intrinsic factor in it will not produce pernicious anemia, or the monkey does not require the anti-pernicious anemia factor. Perhaps the intestinal tract performs a more important function than passive absorption". The same deductions should apply to those humans who fail to develop pernicious anemia after total gastrectomy.

Until data are accumulated as to what happens to the liver principle to patients with total gastrectomy, it is obvious that no further deductions are permissible. Such data required would be: 1. Biologic assay of the liver of a patient who had had total gastrectomy several years prior, (to allow time for depletion) and who had no pernicious anemia. If the quantitative content of the liver was normal, several explanations would be possible. Either extragastric intrinsic factor (intestinal) was available, or the anti-pernicious anemia liver material in that individual could be formed without intrinsic factor. If the liver was depleted of the anti-pernicious anemia material, it would appear that that individual did not need the specific liver principle.

The anti-anemic potency of the normal human gut and of that of a patient with Addisonian pernicious anemia in relapse has not been determined. The anti-anemic potency of the intestine of a patient following total gastrectomy has not been determined. All these data are essential before deductions can be made as to the intestinal production of human intrinsic factor. Why anacidity is so intimately related to subsequent loss of gastric intrinsic factor in Addisonian pernicious anemia is difficult to explain. It can be explained as a component part of an inherited dual secretion loss, loss of acid and later loss of intrinsic factor. Although ordinary anacidity per se carries little

hazard in relation to the loss of intrinsic factor, it constitutes a definite hazard for an individual in whose family there is pernicious anemia.

SUMMARY

1. Forty-seven reported cases of supposed pernicious anemia without achlorhydria have been reviewed.

2. None of these has been proved by complete precise criteria to be Addisonian pernicious anemia.

3. It would seem wise to restrict the term pernicious anemia to the true or Addisonian pernicious anemia characterized by absolute anacidity, loss of intrinsic factor and reduction of the specific liver principle.

4. Until precise critical tests have proved that acid secretion can persist in pernicious anemia, the presence of acid in any case must be considered as ruling out Addisonian pernicious anemia. The existence of true pernicious anemia without anacidity as yet cannot be accepted.

REFERENCES

1. Cornell, B. S.: Medicine, 6: 375, 1927.
2. Shaw, M. E.: Guy's Hosp. Rep., 76: 294, 1926.
3. Ungley, C. C.: Newcastle, M. J., 10: 14, 1929.
4. Levine, S. A., and Ladd, W. S.: Bull. Johns Hopkins Hosp., 32: 254, 1921.
5. Faber, K., and Gram, H. C.: Arch. Int. Med., 34: 658, 1924.
6. Hartfall, S. J.: Guy's Hosp. Rep., 83: 37, 1933.
7. Moore, H., and O'Farrell, W. R.: Brit. M. J., 1: 516, 1933.
8. Wilkinson, J. F.: Quart. Jour. Med., 1: 361, 1932.
9. McPeak, E. M., and Neighbors, DeW.: South. M. J., 20: 926, 1927.
10a. Hurst, A. F.: Guy's Hosp. Rep., 80: 407, 1930.
b. Hurst, A. F.: Quart. J. Med., 1: 157, 1932.
11. Connery, J. E., and Jolliffe, N.: Am. J. M. Sc., 181: 830, 1931.
12. Finney, J. O.: Ann. Int. Med., 12: 1521, 1939.
13. Harvey, E. A., and Murphy, W. P.: Ann. Int. Med., 6: 1393, 1933.
14. Beebe, R. T., and Wintrobe, M. M.: Arch. Int. Med., 51: 630, 1933.
15. Bloch, E.: Deutsches Arch. f. klin. Med., 77: 276, 1903.
16. Weber, A.: Deutsches Arch. f. klin. Med., 97: 165, 1909.
17. Passey, R. M.: Guy's Hosp. Rep., 72: 172, 1922.
18. Von Willebrand, E. A.: Acta. med. Scandinav., 56: 419, 1922.
19. Shackle, J. W.: Guy's Hosp. Rep., 73: 211, 1923.
20. Heath, E. H.: J. A. M. A., 91: 928, 1928.
21. Loewenberg, W., and Gottheil, C.: Deutsche med. Wchnschr., 54: 615, 1928.
22. Grinker, R. R.: Arch. Int. Med., 38: 292, 1926.
23. Seyderhelm, R., and Opitz, G.: Klin. Wchnschr., 7: 205, 1928.
24. Nielsen, O. P.: Ugesk. f. laeger, 103: 1023, 1941; abstr., Acta med. Scandinav., 108: 421, 1941.
25. Levin, A. L.: Am. J. Digest Dis. & Nutrition, 1: 240, 1934.
26. Davidson, L. S. P.: Brit. M. J., 1: 182, 1933.
27. Castle, W. B., Heath, C. W., and Strauss, M. B.: Am. J. M. Sc., 182: 741, 1931.
28. Alsted, G.: Acta. med. Scandinav., 82: 288, 1934.
29. O'Brien, G. T.: Discussion of paper by Moore and O'Farrell.[7]
30. Sanford, C. H.: Ann. Int. Med., 9: 189, 1935.

31. MANSON-BAHR, P.: Tr. Roy. Soc. Trop. Med. & Hyg., **34:** 347, 1941.
32. RHOADS, C. P., AND CASTLE, W. B.: Am. J. Path. (Supp.), **9:** 813, 1933.
33. WOLTMAN, H. W., AND HECK, F. J.: Arch. Int. Med., **60:** 272, 1937.
34. SNAPPER, I.: Chinese Lessons To Western Medicine, Interscience Pbls., Inc., N. Y., 1941, page 286.
35. GOLDHAMER, S. M.: Am. J. M. Sc., **195:** 17, 1938.
36. STURGIS, C. C., AND GOLDHAMER, S. M.: Ann. Int. Med., **12:** 1245, 1939.
37. CASTLE, W. B., RHOADS, C. P., LAWSON, H. A., AND PAYNE, G. C.: Arch. Int. Med., **56:** 627, 1935.
38. CASTLE, W. B., TOWNSEND, W. C., AND HEATH, C. W.: Lancet, **1:** 1062, 1930.
39. BARKER, W. H., AND HUMMEL, L. E.: Bull. Johns Hopkins Hosp., **64:** 215, 1939.
40. Year Book of General Medicine, 1933, Editorial note, page 341.
41. STRAUSS, M. B., AND CASTLE, W. B.: Am. J. M. Sc. **185:** 539, 1933.
42. BUSSABARGER, R. A., IVY, A. C., WIGODSKY, H. S., AND GUNN, F. D.: Ann. Int. Med., **13:** 1028, 1939.
43. WILLS, L., AND EVANS, B. D. F.: Lancet, **2:** 416, 1938.
44. COHN, E. J., MCMEEKIN, T. L., AND MINOT, G. R.: Tr. A. Am. Physicians, **45:** 343, 1930.
45. DAKIN, H. D., AND WEST, R.: J. Biol. Chem., **109:** 489, 1935.
46a. HURST, A. F., ET AL.: Proc. Roy. Soc. Med., Lond., 1924–25 xviii, Section Neurol., 21–27.
b. HURST, A. F.: Brain, **48:** 218, 1925.
47. WEBER, F. P., AND HUBER, H.: Acta. Med. Scandinav., **104:** 543, 1940.
48. FOX, H. J., AND CASTLE, W. B.: Am. J. M. Sc., **203:** 18, 1942.
49. SCHEMENSKY, W.: Ztschr. f. klin. Med., **128:** 428, 1935.
50. UOTILA, U.: Acta. med. Scandinav., **95:** 415, 1938.
51. MEULENGRACHT, E.: A Symposium on the Blood, Univ. of Wis. Press, Madison, 1939, pages 72–81.
52. JACOBSON, W.: J. Path. & Bact., **49:** 1, 1939.
53. ALLEN, A. W.: Am. J. Surg., **40:** 35, 1938.
54. MAISON, G. L., AND IVY, A. C.: Proc. Soc. Exper. Biol. & Med., **31:** 554, 1934.
55. GEIGER, A. J., GOODMAN, L. S., AND CLAIBORN, L. N.: Yale J. Biol. & Med., **13:** 259, 1940.
56. A personal communication from Dr. Connery says this patient lived until 1942, dying of carcinoma of the face.

DISEASE IN THE TROPICAL WAR ZONES

III. The Diseases of the Mediterranean Basin and of Tropical Africa

Ernest Carroll Faust

Professor of Parasitology, Department of Tropical Medicine, Tulane University of Louisiana, New Orleans, La.

INTRODUCTION

Although the writer has indicated in the first paper of this series (Faust, 1943) that the Mediterranean Basin and Tropical Africa comprise two nosographically different areas, it will be convenient to consider them together in this paper. In the first place, they are essentially contiguous. Moreover, some of our troops are quartered in Tropical Africa and have been or may be sent to North Africa. Finally, our air transport service has several landing fields in the more tropical part of the African Continent, beginning on the west coast and continuing through the Sudan to Egypt, thence to the Middle East and India. Thus, the entire region considered in this paper, from the tropical heart of Africa up into Southern and Southeastern Europe and the Near East is today of great medical importance because of its strategic military significance and the daily intercommunication from north to south and from east to west. Moreover, as military personnel from these areas are invalided home, more and more cases of infections acquired in these war zones will be seen by civilian physicians here at home.

THE DISEASES OF THE AFRO-MEDITERRANEAN AREAS

Viewing this territory as a whole there are relatively few human diseases which are not found somewhere within these two areas. The diseases with most extensive distribution are malaria, typhoid fever, the dysenteries, the intestinal helminthiases, Bancroft's filariasis, schistosomiasis, the leishmaniases, the typhus group of fevers, dengue, leprosy and the venereal diseases. These and other diseases will now be considered briefly.

Malaria. As in other tropical war zones malaria on the Continent of Africa and along the Mediterranean coast of Europe and the Near East constitutes the most widespread hazard and the most serious infectious disease for our military forces (Fig. 12). In tropical Africa, along the north African coast, in Palestine and Syria, in the region of Salonika in Greece and around the Black Sea it is hyperendemic. In the lower Nile valley, Sicily, Italy, Sardinia, Corsica, throughout the Balkans and extending through to the Caucasus this disease has for centuries been a major encumbrance on the population. Moreover, in mildly endemic form the disease extends as far south as the Union of

South Africa and as far north as the Channel ports of France and the Low Countries and throughout vast expanses of the U. S. S. R.

Throughout tropical Africa the one important mosquito which transmits malaria is *Anopheles gambiae*. In the Mediterranean basin the most dangerous species is *Anopheles maculipennis* var. *labranchiae*. Along the West Coast and in the heart of Africa malaria behaves as it does in any strictly moist tropical region, i.e., it is hyperendemic. In the Mediterranean basin it is

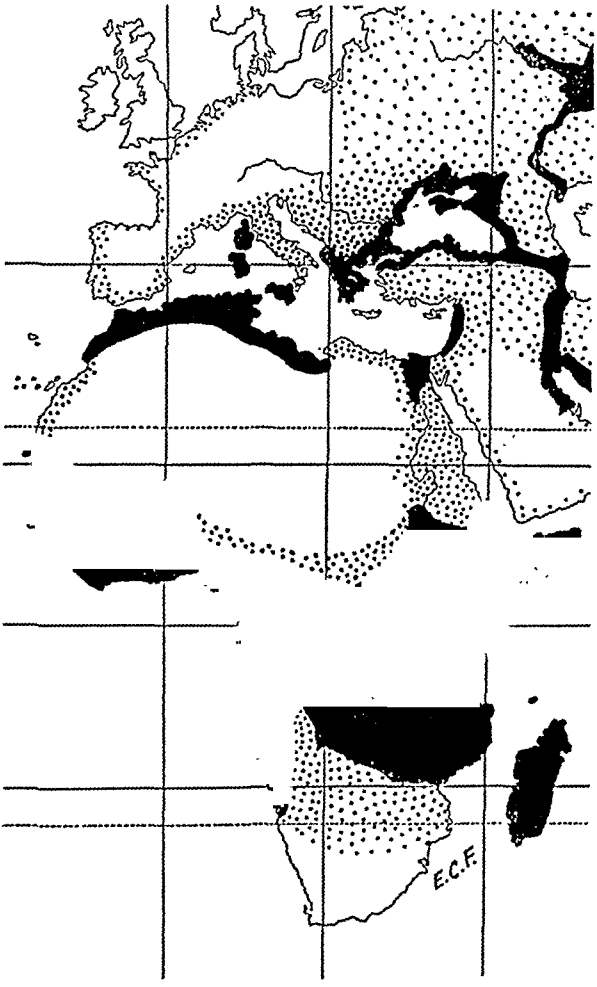


FIG. 12. Map of Africa, Europe and the Near East showing the distribution of malaria. Areas of hyperendemicity are in solid black; areas of milder endemicity are stippled (original).

similar to the disease as it exists in the southeastern United States. While there is extensive tertian malaria both in the more temperate and in the hot climates of Africa and Europe, and while quartan malaria is also present as a major infection in Central Africa and as a minor disease entity elsewhere, the serious, incapacitating and at times fatal infection is that produced by *Plasmodium falciparum*, the so-called estivo-autumnal, malignant or tropical parasite.

Falciparum malaria is particularly serious because of its very rapid development in the viscera without a comparable indication in the peripheral blood of its fulminating growth. This parasite tends to accumulate in the blood sinuses of the liver, spleen and bone marrow, and to agglomerate and block the blood capillaries in the lungs, adrenal cortex and the brain. This is probably the only type of malaria which is a primary cause of death in the average infected individual.

In certain groups of our military forces in West and North Africa malaria has developed to severe epidemic proportions in spite of precautions taken by the medical and sanitary officers in charge of these troops. The British Near East medical command experienced this same hazard earlier because of their campaigns in Ethiopia, Somaliland, Eritrea and Libya. They came to the conclusion on a basis of extensive experience that in hyperendemic malarious territory such as they encountered it was necessary to give not less than 0.1 gm. (1½ grains) of atabrine daily six days a week (or 0.6 gm. of quinine daily if available) as suppressive treatment to keep troops clinically free of the disease. Moreover, it has been found desirable to begin atabrine "prophylaxis" approximately two weeks before the personnel are exposed to infection, so that their atabrine blood level will be high enough to control the malaria parasites once they are introduced by the infected mosquito.

Curative treatment of clinical cases, either by the standard quinine treatment or full therapeutic doses of atabrine, has not been found to be eminently successful for patients in hyperendemic areas, probably first of all because the patient has been greatly depleted physically and cannot develop an adequate phagocytic defense against the malaria parasites. His removal to a cooler climate, with adequate rest and nourishment, frequently provides the necessary stimulus for overcoming the infection. Moreover, there is some evidence that plasmochin as an adjuvant in the treatment of malaria not only kills the gametocytes, thus preventing new infection in the mosquito, but reduces the relapse rate in the patient.

Malaria in tropical Africa is a major problem throughout the year. In North Africa, Southern Europe and the Near East new infections decrease with the advent of cooler weather in the fall and are not a major medical problem during the cold winter months, even though the parasites may remain viable in hibernating mosquitoes. These epidemiologic findings have a very significant bearing on military campaigns in the Mediterranean basin.

Cholera. This disease is not known to occur west of lower Iraq on the Persian Gulf, and at the present time is not a medical problem in the Mediterranean or African war zones.

Typhoid fever. This disease is prevalent throughout Africa, Southern and Southeastern Europe and the Near East. It is reported by epidemiologists and practicing physicians to be particularly important in the Belgian Congo,

in Kenya, Tanganyika, Northern Rhodesia, North Africa, Yugoslavia, Greece, the Near East (Palestine, Syria, Transjordania) and the Arabian peninsula. No general immunization of native populations is carried out in these countries, and sanitary sewage disposal is lacking except in individual homes and hotels owned by the better class Europeans. Furthermore, the tremendous number of filth flies breeding around the homes and in the bazaars contributes largely to the epidemic spread of the disease.

In French Morocco, Algeria and Tunisia the Pasteur Institutes have made splendid contributions to the diagnosis and epidemiology of typhoid and other enteric diseases, but the health departments of these countries have not made practical application of the information provided.

Although sanitation in Southern Europe is considerably better than in Africa and the Near East, much remains to be accomplished. In Yugoslavia and other Balkan countries human nightsoil is commonly used to fertilize garden crops. Bottled mineral water, beer and light wines are depended on for drinking purposes in place of piped water from city sources. This in itself indicates the lack of dependence placed on regular water supplies.

Bacillary dysentery. This infection is reported to be particularly important as a disease entity throughout Central and North Africa. It is very common in Angola (south of the Belgian Congo), in the Congo basin, in Kenya, Tanganyika and Northern Rhodesia, along the coast of North Africa from Morocco to Egypt and throughout the Near East. It is prevalent in the Balkans but is apparently a less serious and less prevalent disease in Southern Europe. Since most of the reports are scattered or are based on clinical diagnosis, the types of *Shigella* involved as causative agents are not commonly reported. There is also the likelihood that bacillary dysentery may frequently be confused with amebic dysentery or with acute food poisoning, while in many localities no attempt is made to distinguish the dysenteries on the basis of their etiology.

Amebiasis. Clinical amebiasis is widespread throughout tropical Africa, the north African coast, the Near East, Asia Minor, the Arabian peninsula, Iraq and Iran (Fig. 13). Infection with the etiologic agent, *Endamoeba histolytica*, is extensive from the southern tip of Africa as far north as Sweden and Finland. In Central Europe it frequently occurs without dysenteric manifestations and most of the infected individuals are referred to as "carriers". French workers, particularly Brumpt (1928), have sponsored the view that certain strains of *E. histolytica* are non-pathogenic and have even gone so far as to give them a separate species designation. However, critical experimental evidence favoring Brumpt's hypothesis is lacking. In the Balkans amebiasis is much less common than bacillary dysentery.

Throughout the hyperendemic areas of amebiasis in Africa, the Near East and the Middle East the disease occurs quite commonly in acute dysenteric

form, frequently with the complication of amebic liver abscess. This was the picture observed by Kartulis in Cairo in 1886 and has not been appreciably altered since that day. Today, however, we know that this same type of acute infection extends from the West Coast of Africa throughout the warmer portions of the entire area (see map). In Southern Europe acute amebic dysentery also occurs, but is less frequent. Here there is a wide range in symptoms resulting from infection, including rectal, cecal and generalized manifestations, depending perhaps on the quantity of amebae which invade the bowel wall,

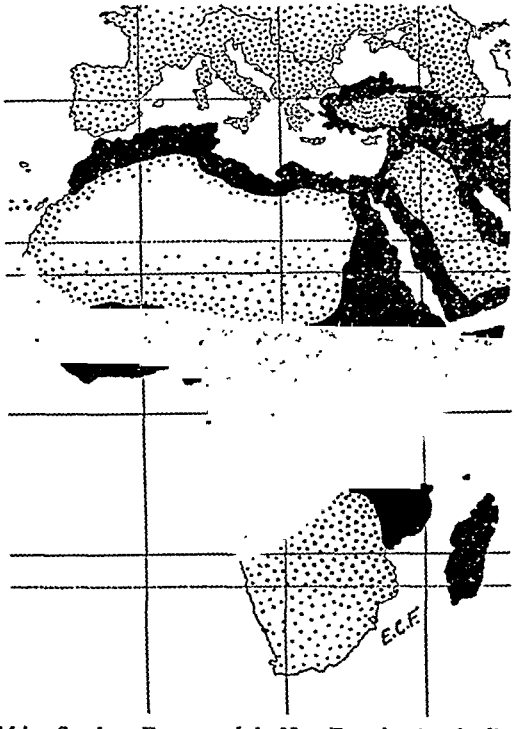


FIG. 13. Map of Africa, Southern Europe and the Near East showing the distribution of amebiasis Areas of hyperendemicity are in solid black; areas of milder endemicity are stippled (original).

on the pathogenic index of the organism and on the threshold of resistance of the individual to infection. White persons who sojourn in hyperendemic areas of amebiasis even for a short time, almost invariably acquire acute amebic dysentery.

Since the investigations of Wenyon and O'Connor (1917) in the Near East conservative opinion has looked upon the fly as the common transmitter of the infection in this area. Anyone who has ever visited in Leopoldville, Monrovia, Oran, Cairo, Beirut, Addis Ababa, Aden or Bagdad can testify to the pestilence of filth flies, especially during the warm dry months of the

year. In the absence of other direct evidence the fly-transmission hypothesis in this area is the most convincing.

Intestinal helminthiases. Ascariasis, hookworm disease, strongyloidiasis and whipworm infection are common throughout Africa, much of southern Europe and the Near East, while tapeworm infections occur in considerable amounts in particular areas. In tropical Africa certain fluke infections of the bowel are locally important.

Ascariasis is probably the most prevalent disease in native children in Central, West and North Africa, as well as in Southeastern Europe and the Near East. In children under ten years of age the incidence frequently runs as high as 90 to 100 per cent. As a result of the fouling of the dirt floors of the homes and the dooryards with children's feces the eggs of *Ascaris* are seeded in these locations and after a few weeks incubation are infective. Exposure consists in taking these fully embryonated eggs into the mouth on soiled fingers, food or play objects. In these hyperendemic environments children are constantly subject to reinfection and adults to a somewhat lesser degree.

En transit through the lungs the larvae of *Ascaris*, if present in appreciable numbers, produce an atypical pneumonia, due to multiple hemorrhage into the air sacs as the larvae break out of the pulmonary capillaries and to polymorphonuclear leukocyte infiltration in each site. In the intestine a mass of worms may produce acute obstruction, appendicitis with peritonitis, or single worms may penetrate into the liver parenchyma or even reach the pleural cavity. Competent physicians in tropical Africa have testified to the high death toll among children resulting either from pulmonary or intestinal ascariasis.

While ascaricidal drugs, as caprokol, are very satisfactory in eliminating the worms from the bowel, the major problem is one of educating infected populations concerning the danger of promiscuous defecation.

Hookworm infection. Within the two zones considered in this paper there are two different species of hookworms which produce intestinal infection in man (Fig. 14). In the tropical belt, approximately between the Tropic of Cancer and the Tropic of Capricorn, the prevalent and almost exclusive species is *Necator americanus*, the same type which is widespread in the American Tropics. Along the North Coast of Africa, in the Nile valley, in Sicily, Italy, Sardinia, Corsica and in a few local foci elsewhere in Europe the sole species is *Ancylostoma duodenale*, the hookworm which was discovered in Milan, Italy in 1838 and was investigated intensively in Alexandria and Cairo. Due to promiscuous defecation on the soil, especially in moist, shaded warm locations, the eggs have an opportunity to complete their embryonation in one to two days, to hatch, feed and grow, and then to transform into the infective-stage larvae. Human beings walking barefooted on infected soil provide the

opportunity for exposure. From the skin the larvae migrate *via* the lungs to the small bowel, where they become attached to the wall of the small intestine.

By lytic ferments and suction produced by their esophageal muscles they digest the tips of the villi and "milk" the victim's blood through their bodies, far in excess of their nutritional needs. This mechanical loss of blood, unless compensated, is responsible for the microcytic hypochromic anemia which is

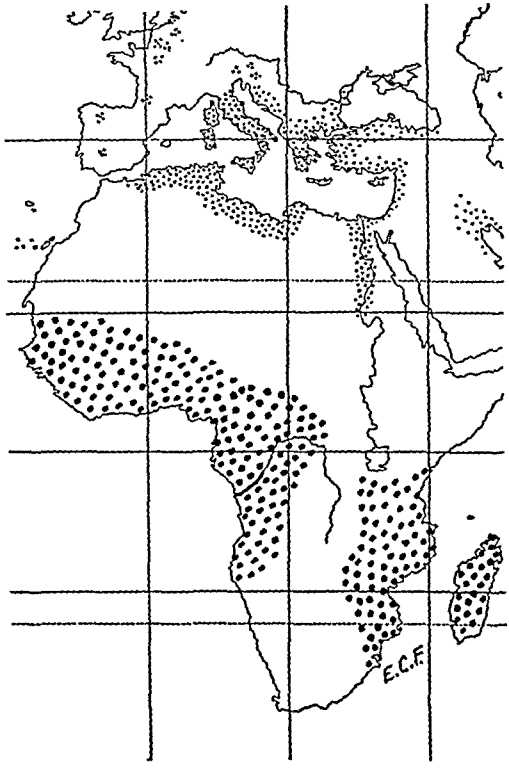


FIG. 14. Map of Africa, Southern Europe and the Near East showing the distribution of human hookworm infections. *Necator americanus* endemic territory is stippled with heavy dots; *Ancylostoma duodenale* territory, with light dots (original).

characteristic of hookworm disease. This explains the "miner's anemia" of Central and Southern Europe and "Egyptian chlorosis". As a result of this anemia a state of cachexia develops. There is increased oxygen want even though the heart becomes hypertrophied and works overtime in an attempt to carry the depleted blood more rapidly to the viscera. In children physical development and sexual maturity are delayed. Except for the heart damage which becomes permanent in hookworm disease of long-standing the disability

is readily combatted by the administration of an efficient anthelmintic, as tetrachlorethylene, together with a well-balanced nutritious diet supplemented with iron.

While mass treatment of hookworm-infected populations will do much to reduce both the incidence and worm burden of the infected group, sanitary disposal of human nightsoil is a necessary supplement to eradicate the infection from the area.

Strongyloidiasis and whipworm infection. The actual incidence of these two infections is not known throughout most of the territory under consideration, but both of these helminthiases are widely distributed in the Mediterranean littoral and in tropical Africa. Treatment of these infections is usually much more difficult than of ascariasis or hookworm infection. Effective control of hookworms will greatly reduce the incidence of these infections as well.

Tapeworm infections. The intestinal tapeworms include *Taenia saginata* (beef tapeworm), *T. solium* (pork tapeworm), *Hymenolepis nana* (dwarf tapeworm) and *Diphyllobothrium latum* (fish tapeworm). *T. saginata* is common in the Mohammedan and Coptic populations of the area, and is highly prevalent in Abyssinia. *T. solium* is practically non-existant in these groups but occurs frequently in Southeastern Europe. *H. nana* has an extensive distribution, particularly among children, in the Mediterranean basin. *D. latum* is primarily found in Northern and Central Europe but extends into the Balkans, and has been reported from Lake Tiberias in the Near East and the lake district of Central East Africa. Moreover, a visceral tapeworm infection, hydatid disease, occurs through the entire territory and is reported to be particularly important in Northern Rhodesia and in the Near East. Efficient treatment for intestinal tapeworm infections was developed by the Egyptians (pomegranate, from which pelletierin is derived) and by the Greeks (male fern, from which oleoresin of aspidium is obtained).

Tapeworms have afflicted the populations of these regions from earliest historical times. There is no evidence that modern knowledge concerning their epidemiology and control has produced any appreciable reduction in their incidence or distribution.

Schistosomiasis. Two schistosomes (blood flukes) have extensive distributions throughout Africa and the Near East, *Schistosoma haematobium*, which is primarily vesical and pelvic in its pathology, and *S. mansoni*, which primarily involves the large bowel and the liver. *S. haematobium* is widely distributed throughout Africa (Fig. 15), including a large area in West Africa, the Congo basin, North Africa and East Africa from Egypt to the Cape. It also occurs in Palestine and Syria, in a few foci in Arabia and in Iraq. *S. mansoni* (Fig. 15) has several important foci of infection in Africa but probably is not endemic east of Suez.

These infections are incubated in certain species of snails which breed in water contaminated with human feces. The infective stage for man is a fork-tailed larva (cercaria) which swims in the water and becomes attached to the skin of persons who wade or bathe in "infected water". The larvae burrow down to the cutaneous blood vessels which they enter and then are carried in the blood stream *via* the right heart to the lungs. They squeeze through the pulmonary capillaries, pass through the left heart and out into the systemic

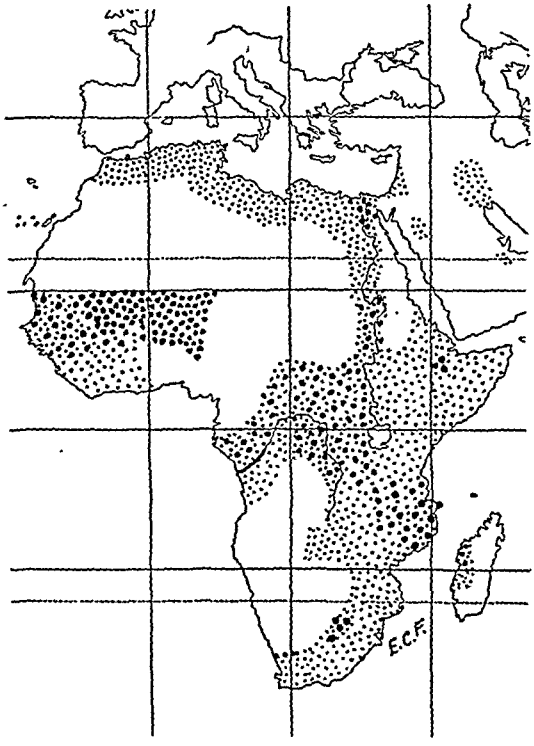


FIG. 15. Map of Africa, Southern Europe and the Near East showing the distribution of blood fluke infections (schistosomiasis). Schistosomiasis mansoni endemic territory is stippled with heavy dots; schistosomiasis haematobia territory, with light dots (original).

circulation. The majority reach the portal blood vessels *via* the mesenteric capillaries, grow as they feed on whole blood within the intrahepatic portal vessels and then migrate out against the portal blood stream. *S. mansoni* usually settles down in the small mesenteric venules draining the large bowel; *S. haematobium* migrates *via* mesenteric veins, hemorrhoidals and pudendals into the vesical venules. In these respective sites the worms mature, mate and begin to lay eggs. The eggs escape from the venules and at first filter through the perivascular tissues to be expelled into the lumen of the colon

(*S. mansoni*) or urinary bladder (*S. haemotobium*) together with blood and necrotic tissue. Thus there is schistosomal dysentery or hematuria. Later the eggs remain lodged in the perivascular tissues due to host cell infiltration and become the centers of miliary pseudotubercles.

Although the anatomical sites of these two worms are typically distinct, the damage produced is fundamentally the same, namely general intoxication and fibrosis of vital tissues. In the intestinal type (Manson's schistosomiasis) fibrosis of the colon, cirrhosis of the liver and splenomegaly are the most common sequelae. In vesical schistosomiasis the chronic lesions consist of progressive fibrosis of the urinary bladder with complications involving the genitalia, rectum and lungs.

Treatment consists in intensive use of antimony. Control of these diseases will depend ultimately on the safeguarding of water from contamination with human feces (*S. mansoni*) and urine (*S. haematobium*).

Filariasis. Several species of filaria worms produce human infection in Africa and adjacent regions. Three of these, *Wuchereria bancrofti*, *Onchocerca volvulus* and *Loa loa* are important causes of disease.

W. bancrofti (Fig. 16) has a widespread distribution from Rhodesia and Angola north to the Sahara. It is prevalent in North Africa and along the south and west coasts of Arabia; it also occurs in small foci in Southern Europe. The infective larval stage is transmitted to man by common house mosquitoes. After a period of months the adolescent worms become localized in the lymphatic vessels and lymphoid tissue, especially in the region of the groin and spermatic duct. The adult worms discharge microfilariae which circulate in the peripheral blood, usually at night. Sooner or later tissue reaction to the worms usually takes place, with repeated episodes of lymphangitis, and later fibrosis of the area with lymph varix and elephantiasis. There is no satisfactory therapy. Control consists in the prevention of mosquito breeding around the homes.

Onchocerca volvulus and *Loa loa* have distributions confined to the heart of Africa. They are transmitted to man by certain species of blood-sucking flies. The former filaria produces a subcutaneous tumor within which parent worms are immured. The microfilariae migrate through the lymphatics of the skin and subcutaneous tissues but do not enter the blood stream; frequently they migrate into the tissues of the eye and provoke a reaction leading to impared vision and eventual loss of sight. *Loa loa* adults migrate through subcutaneous tissues producing fugitive swellings. From time to time they cross the front of the eye. Their microfilariae manifest diurnal swarming in peripheral blood. Surgical removal of the adult *Onchocerca volvolus* and *Loa loa* is the indicated procedure. Prevention is not on a satisfactory basis.

A non-filaria worm, *Dracunculus medinensis*, is frequently referred to as a

filaria, although neither in its structure nor life cycle does it resemble a true filaria. This worm has an extensive distribution in French Equatorial Africa, on the West Coast, throughout the Nile valley from the delta to Uganda, and in ports of Arabia and the Persian Gulf coast. Man acquires this infection from swallowing infected *Cyclops* in water previously contamined by human beings who have bathed in the water. On contact with fresh water the larvae escape from gravid female worms which have migrated from the viscera to the skin. There is no satisfactory treatment other than the ancient method of

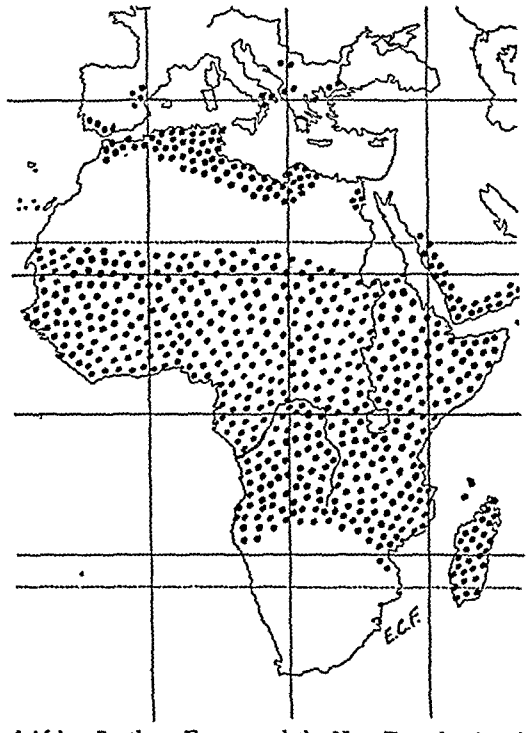


FIG. 16. Map of Africa, Southern Europe and the Near East showing the distribution of Bancroft's filariasis (original).

drawing the female worm little by little out of the subcutaneous tunnel. Except for substituting draw wells for step wells no satisfactory control of this disease has been developed in the areas under consideration.

Leishmaniases. This group of diseases is produced by species of hemoflagellate protozoa belonging to the genus *Leishmania.* Two of these species, *L. donovani* and *L. tropica*, are widely distributed throughout Central and North Africa, Southern Europe and the Near East (Fig. 17).

The etiologic agents are transmitted to man by certain species of sandflies (*Phlebotomus*). In the gut of the sandfly the organisms are each provided with

an anterior flagellum. On injection into the cutaneous bloodstream of man they are engulfed by wandering macrophages, roundup, retract the flagellum and propagate within these and other cells of the reticulo-endothelial system. *L. donovani* produces a visceral infection with a profound reticulo-endotheliosis, neutropenia and erythropenia. *L. tropica* is confined to the superficial tissues, with the production of one or more cutaneous lesions. Treatment consists n the administration of antimony.

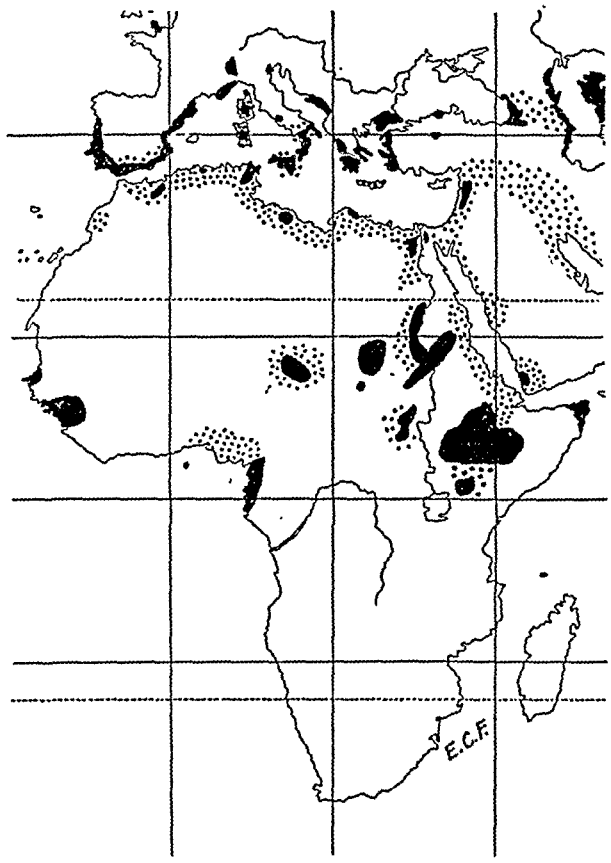


FIG. 17. Map of Africa, Southern Europe and the Near East showing the distribution of leishmaniasis. Areas with endemic visceral leishmaniasis are in solid black; those with cutaneous leishmaniasis are stippled (original).

Because of the wide prevalence of these two types of leishmaniasis in the areas under consideration there is considerable likelihood that American troops quartered in endemic foci will be exposed to bites of infected sandflies and will acquire one or the other of these diseases.

Trypanosomiases. This group of infections is caused by species of hemoflagellate protozoa belonging to the genus *Trypanosoma.* Two of these infections causing human disease occur in Africa, *T. gambiense,* prevalent in the tropical rain-forest areas of West and Central Africa and *T. rhodesiense,* prev-

alent in the Central Eastern plateaus of Northern Rhodesia, Nairobi, Tanganyika, Kenya, Southern Uganda and the Eastern Congo near the lake district.

The etiologic agents are transmitted by certain species of tsetse flies (*Glossina*). The trypanosomes in man (or other definitive hosts, as domestic and wild mammals) are interstitial in their locations. As they multiply they progressively concentrate in the blood stream, lymph nodes and central nervous system. The Rhodesian type is much more fulminating and seldom reaches the third stage before the patient succumbs. Tryparsamide and germanin (Bayer 205) are efficient therapeutics if the infection is treated early in its course. Extensive surveys in the Gambian endemic foci to determine the infected individuals, followed by treatment, have resulted in a remarkable reduction in the incidence of the disease.

The typhus group of fevers. These diseases are produced by species of *Rickettsia.* Two main types occur in the areas under consideration, typhus fever *sensu stricto* and tick typhus. Typhus fever is produced by *R. prowazeki* and has two main varieties, (1) epidemic (exanthematic) typhus due to infection with *R. prowazeki prowazeki*, which is transmitted by human body lice, and (2) endemic (murine) typhus, due to infection with *R. prowazeki mooseri*, which is transmitted by rat fleas. Tick typhus is produced by *R. rickettsi.* Typhus fever is widely distributed throughout Africa, Europe and the Near East (Fig. 18). The louse-borne type is hyperendemic in Morocco, Algiers, Tunis, Egypt, Spain, the Balkans and Poland and in less intensive form is prevalent practically throughout the entire territory. Tick typhus occurs in South and Central Africa and in the Mediterranean basin (fièvre boutonneuse).

These diseases are not only infectious but are at times contagious, due to the long period of viability of the rickettsias present in the arthropod host's excreta. Depending on the type and method of transmission, infection is acquired from the bite of the infected arthropod, by crushing it on the skin, by getting its feces or coxal gland secretions into cutaneous wounds or on mucous membranes, or breathing in rickettsias from air fouled by lice or flea feces. The organisms have a predilection for the epithelial lining of the smaller blood vessels, in the cells of which they multiply. They escape into the lumens of the vessels and produce thrombosis, causing multiple petechial hemorrhages into the perivascular tissues. Following a short incubation period, there is characteristically a high toxic fever succeeded by a slow convalescence in cases which pass the crisis satisfactorily. There is no specific therapy.

Immunization with specific antigens, as the Cox chick embryo tissue vaccine in epidemic typhus fever, has apparently been very effective in preventing infection among American troops in highly endemic areas in North Africa.

Delousing in louse-borne typhus, anti-rat campaign in murine typhus and avoidance of tick infestation in tick typhus areas constitute important preventive procedures.

Plague. This disease is produced by *Pasteurella pestis.* It is enzoötic and from time to time epizoötic in rodents, and from these reservoirs reaches man. Several important foci of human plague exist in Africa and the Near East

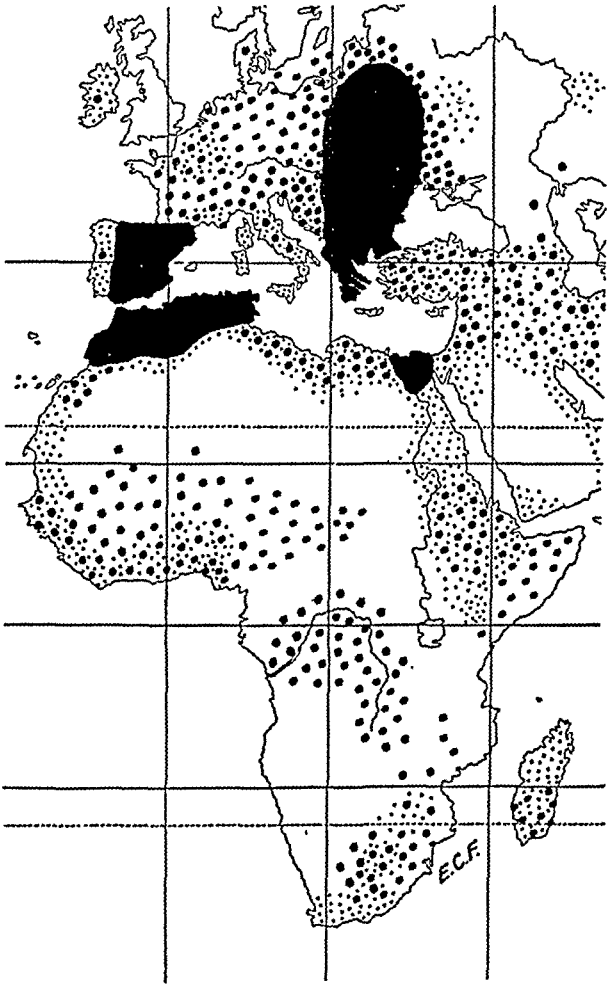


FIG. 18. Map of Africa, Europe and the Near East showing the distribution of typhus fever Louse-borne typhus areas are in solid black (hyperendemic) or heavily stippled (epidemic); rat flea-borne typhus areas are lightly stippled (original).

(Fig. 19), especially in South Africa, Kenya, Madagascar, Morocco and the Nile delta. Usually rodent infection is more widely distributed than that in man.

While man-to-man transmission occurs at times by the respiratory route, human infection is usually acquired from the bite of an infected tropical rat flea (*Xenopsylla cheopis*). A bubo develops in a gland near the site of the

bite. If the pathogens all remain within the bubo (bubonic type), the prognosis is fair to good, but more commonly they get into the blood stream (septicemic type) with or without pulmonary involvement (pneumonic type), whereupon the prognosis is grave. There is no specific therapy. Immunization with the Haffkine vaccine (killed organisms) or Otten vaccine (attenuated living organism) apparently affords considerable protection. Anti-rat campaigns constitute sound prevention in areas where domestic rats constitute the reservoirs of infection.

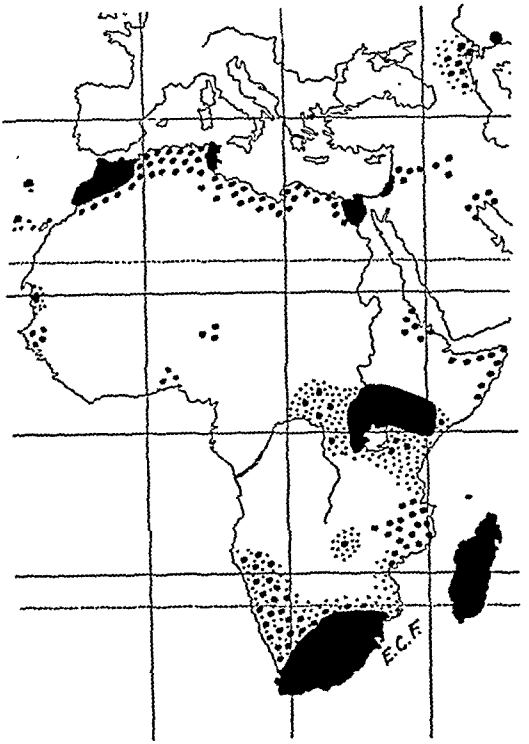


FIG. 19. Map of Africa, Southern Europe and the Near East showing the distribution of plague. Areas of hyperendemicity in the human population are in solid black; areas of less intense human infection are heavily stippled; areas of known rodent plague are lightly stippled (original).

Dengue. This disease is produced by the dengue virus. It is widely distributed throughout the native peoples of Africa, Southern Europe and the Near East (Fig. 20). Infection occurs from bites of infected *Aedes aegypti.* The disease is rarely fatal but usually produces temporary prostration and requires a long period for recovery. There is no specific therapy but intensive anti-*Aedes aegypti* campaigns are effective in reducing the hazard. Military forces in Southern Europe and the Near East are particularly liable to exposure.

Yellow fever. During the past ten years yellow fever in the Eastern Hemisphere has been confined to the tropical belt of Central Africa (Fig. 21). Except on the West Coast most of the cases have occurred in small groups of individuals outside *Aedes aegypti* breeding grounds. The recent epidemic in the Egyptian Sudan (1940) was in an area where *A. aegypti* is not known to exist. Air transport services across Africa have several landing fields within endemic territory. Immunization with the mouse neurotropic strain virus grown on chick embryos has been required of all personnel likely to travel in

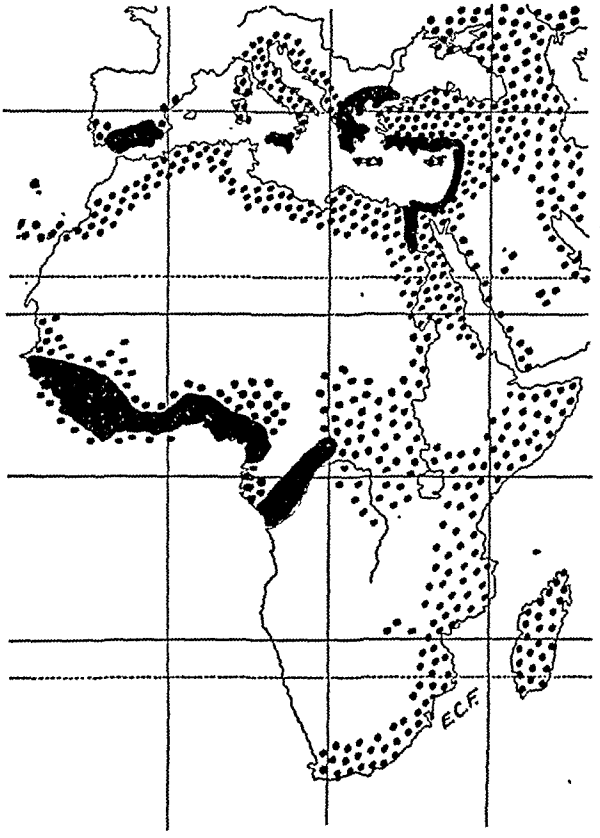


FIG. 20. Map of Africa, Southern Europe and the Near East showing the distribution of dengue. Areas of hyperendemicity are in solid black; areas of milder endemicity are stippled (original).

endemic territory. This has unquestionably prevented infection in large numbers of military and civilian personnel.

Relapsing fever. This infection is produced by spirochetes belonging to the genus *Borrelia.* There are two types, louse-borne (*B. recurrentis*) and tick-borne (*B. duttoni*). The latter has varieties probably as numerous as the species of ticks which are natural transmitters of the infection. In the territory under consideration relapsing fever has a wide distribution. The louse-borne type occurs throughout the northern half of Africa, practically all of

Europe and the Near East. The tick-borne type is endemic in Southern Spain, the Balkans, the Caucasus, Syria and Palestine, North Africa, Ethiopia, practically all of Eastern and South Africa, Madagascar and on the West Coast of Africa. Infection produces an acute febrile disease, frequently with marked jaundice. Neoarsphenamine is an efficient therapeutic. Control consists in delousing measures or in avoiding localities where soft-bodied ticks (*Ornithodorus*) are present.

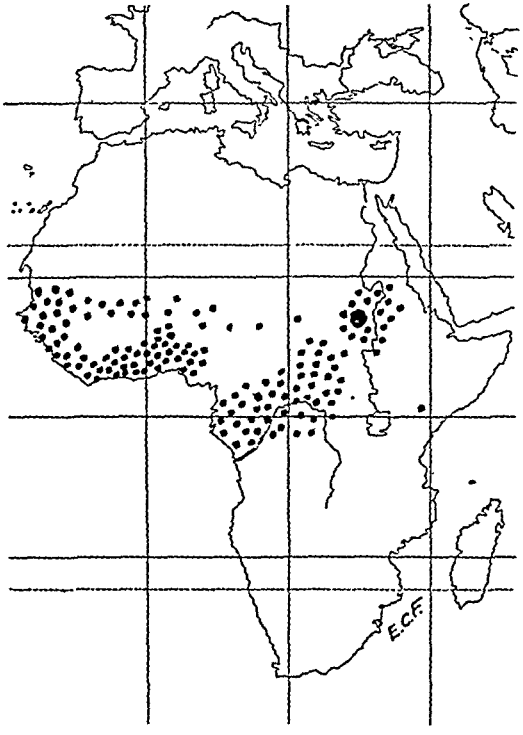


FIG. 21. Map of Africa and adjacent territory showing the endemic areas of yellow fever. The dots represent localities where human cases have been diagnosed since 1932 (original).

Syphilis, yaws and other venereal diseases. Throughout Africa, the Near East and parts of Southern Europe the venereal diseases constitute a major handicap to health and progress. Yaws (frambesia) is very common in the negroid peoples of Tropical Africa. Bejel, also of spirochetal etiology, is prevalent in Palestine, Syria, Lebanon, Transjordan and Iraq. Granuloma inguinale and lymphogranuloma inguinale are also present in the eastern Mediterranean basin.

Leprosy. This disease (Fig. 22) is prevalent in the negroid population from Sierra Leone eastward into the heart of the Congo. On the East Coast it

extends from Eritrea through Portuguese East Africa and Madagascar. It is relatively common in Morocco. It is widely distributed but with low incidence in Rhodesia, the Eastern Congo, the Egyptian Sudan and most of North Africa. Similarly it occurs to a moderate degree in Southern Europe and the Near East.

Cosmopolitan diseases. The acute respiratory infections, including pneumonia and influenza, are particularly noted in the Congo, in the Near

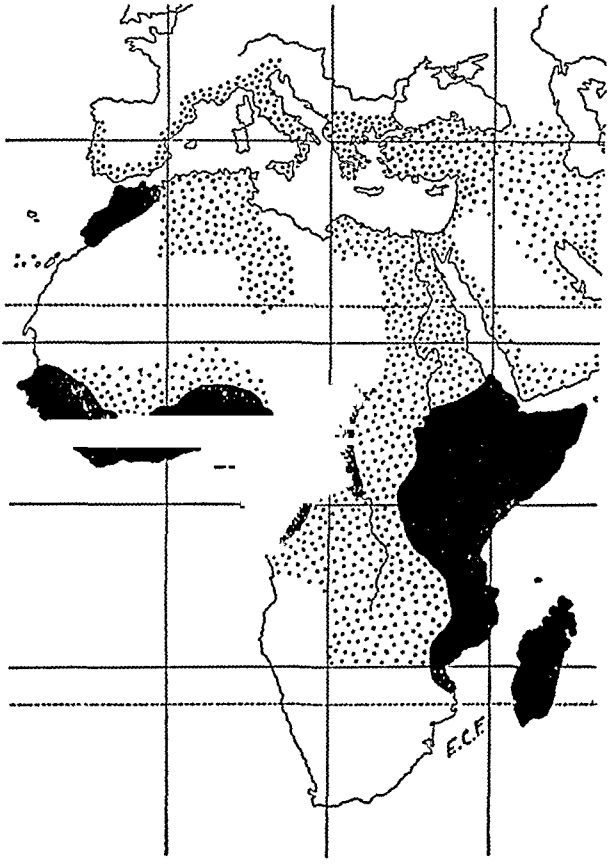


FIG. 22. Map of Africa, Southern Europe and the Near East showing the distribution of leprosy Areas of high incidence are in solid black; those of lighter incidence are stippled (original).

East and Arabia. Pulmonary tuberculosis is common in the Congo, in the Balkans and the Near East. Smallpox occurs in all parts of Africa and the Near East but is hyperendemic in Angola. Undulant fever (Malta fever) is widely distributed throughout the Near East. Among the populations of North Africa, Eritrea, Somaliland and Ethiopia rabies constitutes a very important clinical and public health problem. Mycotic infections, both visceral and cutaneous, are common in the moist Tropics of Africa, while Madura foot is frequently observed in the Near East. Frequently underlying all of these diseases is a preexisting state of malnutrition.

Venomous animals. Throughout Africa there are many species of scorpions which are dangerous to man. When their caudal fang by accident pierces the human skin they introduce toxins which initiate an ascending motor paralysis that at times has a fatal termination. The several Pasteur Institutes in North Africa have polyvalent antivenin for use in treating serious cases.

The most important venenating animals in the Afro-Mediterranean areas are the poisonous snakes. These include two main groups, the true vipers, whose venom primarily produces hemolytic and endotheliolytic action in the victim's body, and the cobras and mambas, whose action is primarily neurotoxic. The most prevalent true vipers are: (1) the adders, with an extensive distribution in Africa, South and Southeastern Europe and Asia Minor; (2) the deadly Russell's viper (daboia), which occurs in Cyprus and Asia Minor; (3) the horned viper, found from North Africa to India, and (4) the deadly efa or phoosa, which is distributed throughout Northeast Africa and the Near East. Several species of cobras, all dangerous, occur from Eastern Africa to Asia Minor. The mambas have an extensive distribution from coast to coast in Tropical Africa. Persons travelling in the jungle, the desert or the mountains of Africa, Southeastern Europe, Asia Minor and the Near East must be constantly on guard to prevent venenation from these and many other dangerous snakes.

VALUABLE REFERENCES ON THE DISEASES OF THE MEDITERRANEAN BASIN AND TROPICAL AFRICA

ADLER, S., THEODOR, O., AND SCHIEBER, H.: Ann. Trop. Med. Parasitol., 31: 25, 1937.

BIRAUD, Y., AND DEUTSCHMAN, S.: Typhus and Typhus-like Rickettsia Infections. Geographical Distribution and Epidemiology. I. Europe and Mediterranean Basin. Epidem. Rept. Health Sec. of the Secretariat, League of Nations, No. 181, pp. 1–16, 1936.

BRUMPT, E.: Trans. R. Soc. Trop. Med. and Hyg., 22: 101, 1928.

CRAIG, C. F., AND FAUST, E. C.: Clinical Parasitology. 3rd ed. Phila., 1943.

FISK, G. H.: Trans. R. Soc. Trop. Med. and Hyg., 32: 645, 1939.

GIRARD, G., AND ROBIC, J.: La Vaccination Antipesteuse avec le Vaccin Vivant E. V. A Madagascar Acta Conventus Tertii de Tropicis Atque Malariae Morbis, Vol. I, 335, 1938.

HACKETT, L. W., AND MISSIROLI, A.: Riv. Malariol., 14: 45, 1935.

JARCHO, S.: War Medicine, 3: 447, 596, 1943.

KARTULIS, S.: Arch. f. path. Anat., 105: 521, 1886.

League of Nations: Annual Epidemiological Report. Corrected Statistics of Notifiable Diseases for the Year 1938, Geneva, 1941.

LÖFFLER, W., AND MOOSER, H.: Schweiz. Med. Wochenschr., 72: 755, 1942.

Medical Department, Pan American Airways—Africa, Ltd.: War Medicine, 3: 484, 619, 1943.

RUTHERFORD, R. B.: Army Med. Bull., 66: 161, 1943.

SLATER, P. R.: Army Med. Bull., 66: 137, 1943.

SOPER, F. L.: Yellow Fever. In "The Cyclopedia of Medicine, Surgery and Specialties," XV, 1986, 1940.

STRONG, R. P.: Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. 2 vols., Phila., 1943.

WENYON, C. M., AND O'CONNOR, F. W.: Human Intestinal Protozoa in the Near East. London and New York, 218 pp., 1917.

WHAYNE, T. F.: Army Med. Bull., 65: 50, 1943.

The roentgenograms were interpreted independently by the two authors and minor variations in interpretation were subsequently reconciled by jointly studying the films. All interpretations were completed without the interpreters knowing whether the subject had been "sick" or "immune" on the motion test. This information was later obtained from the data kept by the trained personnel operating the motion testing device. Their classification as to whether the subject was "sick" or "immune" on the test was accepted without reservation and in this light it must be remembered that the classification of "sick" included all the variations from pallor, sweating and mild nausea to severe vomiting.

The criteria for determining pylorospasm are controversial. We use the following criteria: (a) Pylorospasm was considered to be present *before motion testing* when gastric tone was good, peristalsis present, and no barium had entered the duodenum. (b) Pylorospasm was considered to be present *after motion testing* when gastric tone and peristalsis appeared adequate but no barium appeared to have recently entered the duodenum.

In regard to our first criterion it should be stated that the subjects were fluoroscoped from three to five minutes after ingestion of the barium meal. Whether the lack of emptying during that period in the presence of good gastric tone and peristalsis constitutes adequate evidence for pylorospasm is questionable. However, the observation does differentiate two groups of subjects. In regard to the second criterion, it will be noted later that about half of the subjects after being subjected to motion had no barium in the distal duodenum or the proximal or mid-jejunum but did have barium in the distal jejunum or ileum (interval pattern). After motion, pylorospasm was not considered to be present if barium was present in the duodenal cap or proximal duodenum; it was considered to be present if barium was absent from these parts. This criterion is also open to question but permits a differentiation between groups of subjects.

RESULTS

Twenty-eight of the 100 subjects were classified as having become "sick" and 72 were classified as "immune" (showed no signs and admitted no symptoms of motion sickness). This incidence of 28% "sick" on the test corresponds closely to the incidence of sickness produced by this same device in a series of several hundred subjects who were not studied roentgenographically. Thus, the barium meal did not influence the occurrence of motion sickness on the testing device.

Observations of gastric tone, peristalsis, pylorospasm, progress and distribution of the barium meal are recorded as noted before and after testing. These data are then compared to determine changes in each subject incident to testing.

The subjects are then grouped on a basis of whether they were "motion sick" or "motion immune" and the data compared by groups.

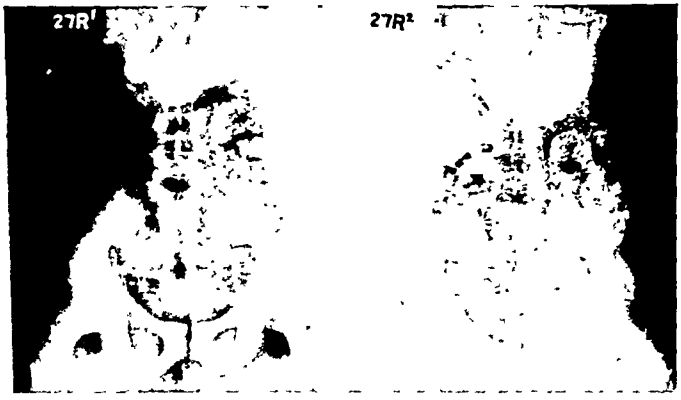


FIG. 1. The pre-motion test film ($27R^1$) illustrates good gastric tone, peristalsis present and no evidence of pylorospasm. The subject completed the full 20 minutes on the motion device and was classified as "immune" because he showed no signs and admitted no symptoms of motion sickness. The film taken immediately after testing ($27R^2$) shows no noteworthy change in gastric tone or peristalsis. There is no evidence of pylorospasm and the barium is normally distributed throughout the small intestine.

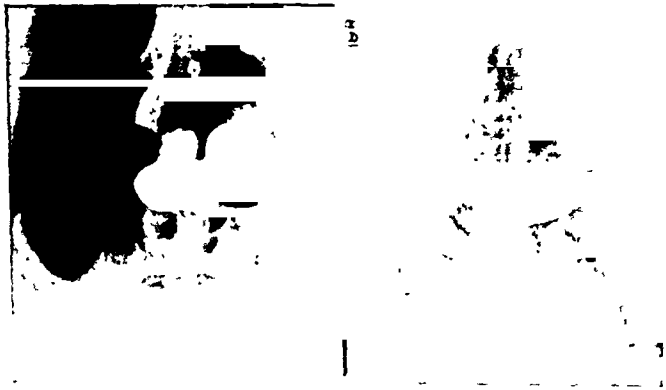


FIG. 2. The pre-motion test film on the left ($19R^1$) illustrates good gastric tone, active peristalsis, no evidence of pylorospasm and beginning emptying of barium from the stomach. This subject developed pallor, sweating and severe nausea after only 3 minutes of motion testing. The test was stopped before vomiting occurred. The film on the right ($19R^2$) was taken immediately after testing and shows the following changes. loss of gastric tone, absence of peristalsis and pylorospasm.

Incidentally, no organic disease of the stomach or small bowel was found in any of the 100 subjects and the individual variations in shape and position of the stomach corresponded to their habitus.

A. *Gastric tone.* Table 1 records the data on gastric tone in all 100 subjects. Tone was recorded as good or poor in each subject before testing. After testing the tone either appeared the same as before testing or it increased or

decreased. The data in this table is further classified so that gastric tone before testing and changes incident to testing can be compared in the "immune" and "sick" subjects.

It will be noted that 11 (15.3%) of the 72 well subjects and 5 (17.8%) of the 28 sick subjects showed poor gastric tone before testing. Thus the condition of gastric tone before testing bears no relationship to the production of "sickness" on this motion testing device. In other words poor gastric tone before testing does not predispose to motion sickness nor does good gastric tone before testing prevent the development of motion sickness.

When changes in gastric tone incident to testing are considered it can be seen that 70 (70%) subjects showed no change, 24 (24%) showed a decrease in tone and only 6 (6%) showed an increase. Now, if these changes are compared in the light of whether the subjects were "sick" or "immune" it

TABLE 1

Gastric tone before motion testing and changes in gastric tone after testing in 100 subjects

CHANGE IN GASTRIC TONE	GASTRIC TONE GOOD BEFORE TESTING				GASTRIC TONE POOR BEFORE TESTING				TOTAL				GRAND TOTAL	
	"Immune" subjects		"Sick" subjects		"Immune" subjects		"Sick" subjects		"Immune" subjects		"Sick" subjects			
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Increase	1	2	1	4	3	27	1	20	4	6	2	8	6	61
Decrease	11	18	13	57	Impossible to determine				11	15	13	46	24	24
No change	49	80	9	39	8	73	4	80	57	79	13	46	70	70
Total	61	100	23	100	11	100	5	100	72	100	28	100	100	100

can be seen that 4 (6%) of the "immune" subjects and 2 (8%) of the "sick" subjects showed an increase in gastric tone. This total of 6 subjects is too small a number to be of much significance but it demonstrates that increase in gastric tone can occur during the twenty minutes of motion testing and this increase bears no relationship to "sickness" or "immunity".

Although only 24% of all the subjects tested showed a decrease in gastric tone it can be noted this occurred much more frequently in those who became "sick" as follows: 13 (46.4%) of the 28 "sick" subjects as compared with 11 (15.3%) of the 72 "immune" subjects showed a decrease in gastric tone. In other words, over three times as large a proportion of "sick" subjects as of "immune" subjects had a decrease in gastric tone. The difference is statistically significant since a difference this large would occur by chance along about once in 1,000 times.

B. *Gastric peristalsis.* Gastric peristalsis was recorded in the same manner

as gastric tone with the exception that instead of being considered poor or good it was recorded as present or absent. Table 2 presents the data on peristalsis in the same manner that the data on gastric tone is presented in table 1. The findings in respect to peristalsis closely parallel those observed in relation to gastric tone.

Peristalsis appeared to be absent before testing in 18 (25%) of the "immune' subjects and 6 (21.4%) of the "sick" subjects. Peristalsis was present before testing in the remaining 54 "immune" subjects and 22 "sick" subjects. After testing, only 12 (22.2%) of the 54 "immune" subjects showed a decrease in peristalsis as compared with 16 (73%) of the 22 "sick" subjects. Thus a decrease in peristalsis occurred 3 times as frequently in the "sick" as compared to the "immune" subjects. This difference is highly significant statistically, there being less probability than 1 in 10,000 of a difference this large being due to chance alone.

TABLE 2

Peristalsis before motion testing and changes in peristalsis after testing in 100 subjects

CHANGE IN PERISTALSIS	PERISTALSIS PRESENT BEFORE TESTING				PERISTALSIS ABSENT BEFORE TESTING				TOTAL				GRAND TOTAL	
	"Immune" subjects		"Sick" subjects		"Immune" subjects		"Sick" subjects		"Immune" subjects		"Sick" subjects			
	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Increase	1	2	0	0	3	17	1	17	4	6	1	4	5	5
Decrease	13	23	16	73	Impossible				13	17	16	57	29	29
No change	40	75	6	27	15	83	5	83	55	77	11	39	66	66
Total ..	54	100	22	100	18	100	6	100	72	100	28	100	100	100

Only 5 out of the 100 subjects showed an increase in peristalsis following the motion test. One of these became "sick" and 4 did not.

C. *Correlation between peristalsis and gastric tone.* Table 3 presents the combined data on gastric tone and peristalsis in relation to the presence or absence of motion sickness as produced on the testing device. Thirteen (46.4%) of the 28 "sick" subjects as compared with 6 (8.3%) of the 72 "immune" subjects showed a decrease in both gastric tone and peristalsis following the motion test. That is to say, over 5 times as large a proportion of "sick" subjects as of "immune" subjects showed a decrease in both gastric tone and peristalsis. This difference is highly significant statistically.

Forty-eight (66.6%) of the "immune" subjects and 11 (39.3%) of the "sick" subjects showed no change with testing in either gastric tone or peristalsis. One of the "immune" subjects and 1 of the "sick" subjects showed an increase in both gastric tone and peristalsis.

Disregarding whether the subjects were "sick" or "immune" there is a fairly high correlation between changes in gastric tone and changes in peristalsis. Eighty (80%) of the 100 subjects showed the same change (or no change) in peristalsis and gastric tone when motion tested; 19 (19%) showed no change in one but an increase or decrease in the other; only 1 showed an increase in gastric tone with a decrease in peristalsis.

D. *Pylorospasm.* The presence or absence of pylorospasm was recorded before testing as well as after testing. Pylorospasm was present before testing in 26 subjects. Twenty of these were "immune" to the motion test and 6 became "sick". That is, 27.8% of the "immune" as compared with 21.4% of the "sick" subjects had pylorospasm before testing, a difference which is statistically insignificant.

Pylorospasm was present after testing in 35 of the 100 subjects. Twenty-three of these were "immune" to the test and 12 were "sick". That is, 31.9%

TABLE 3

Changes in gastric tone and peristalsis in 100 subjects before and after being subjected to the motion test

CHANGE IN GASTRIC TONE	"IMMUNE" SUBJECTS			"SICK" SUBJECTS			TOTAL			GRAND TOTAL
	Change in peristalsis									
	Increase	Decrease	No change	Increase	Decrease	No change	Increase	Decrease	No change	
Increase	1	0	3	1	1	0	2	1	3	6
Decrease	0	6	5	0	13	0	0	19	5	24
No change	3	6	48	0	2	11	3	8	59	70
Total ..	4	12	56	1	16	11	5	28	67	100

of the "immune" subjects as compared with 42.8% of the "sick" subjects had pylorospasm after testing, a difference which is statistically insignificant.

In addition to pylorospasm being present or absent both before and after testing it is obvious that it can change during testing. It can be seen from table 4 that when a change in pylorospasm from absent to present or present to absent occurred during testing, it occurred irrespective of whether the subject became "sick" or not. In other words, these changes in the occurrence of pylorospasm bore no relationship to the occurrence of "sickness".

E. *Intestinal progress.* Progress of the barium meal through the intestine both before and after testing was estimated fluoroscopically or roentgenographically. In no instance did progress of the barium meal exceed that which could be considered normal. Therefore, progress was classified as either normal or less than normal both before and after testing. This classification allows for estimating the change in intestinal progress of the barium meal with testing.

Table 5 shows that 70.8% of the "immune" and 78.6% of the "sick" subjects had normal intestinal progress before testing. This is a percentage difference of no significance. Neither was there any significant difference between the change in intestinal progress from normal to less than normal with testing in the "immune" or "sick" group of subjects. In 100% of the "sick" subjects who had less than normal intestinal progress before testing

TABLE 4

The incidence of pylorospasm in 100 subjects before and after being subjected to the motion test

CHANGE IN PYLOROSPASM WITH TESTING	PYLOROSPASM PRESENT BEFORE TESTING				PYLOROSPASM ABSENT BEFORE TESTING				TOTAL				GRAND TOTAL	
	"Immune" subjects		"Sick" subjects		"Immune" subjects		"Sick" subjects		"Well" subjects		"Sick" subjects			
	No.	%	No	%	No	%	No	%	No	%	No	%	No	%
Absent to present	Impossible				16	30.8	9	41	16	22.2	9	32	25	25
Present to absent	13	65	3	50	Impossible				13	18.1	3	11	16	16
No change	7	35	3	50	36	69.2	13	59	43	59.7	16	57	59	59
Total	20	100	6	100	52	100	22	100	72	100	28	100	100	100

TABLE 5

Changes in the relative intestinal progress of the barium sulphate meal in 100 subjects before and after being subjected to the motion test

CHANGE IN INTESTINAL PROGRESS WITH TESTING	INTESTINAL PROGRESS NORMAL BEFORE TESTING				INTESTINAL PROGRESS LESS THAN NORMAL BEFORE TESTING				TOTAL				GRAND TOTAL	
	Well subjects		Sick subjects		Well subjects		Sick subjects		Well subjects		Sick subjects			
	No.	%	No	%	No	%	No	%	No	%	No	%	No	%
From less than normal to normal.	Impossible				17	81	6	100	17	24	6	21	23	23
From normal to less than normal.	10	20	4	18	Impossible				10	14	4	15	14	14
No change	41	80	18	82	4	19	0	0	45	62	18	64	63	63
Total	51	100	22	100	21	100	6	100	72	100	28	100	100	100

the intestinal progress after testing changed to normal. This same change to normal occurred in 81% of the "immune" subjects who had less than normal intestinal progress before testing. In summary it can be said there was no significant difference in the type of change of intestinal progress with testing when the "immune" group was compared to the "sick" group.

F. *Interval pattern.* It was noted in 47 of the total 100 subjects that after

testing very little or no barium appeared in the duodenum or proximal jejunum, although barium was present in the stomach, distal jejunum and ileum. This condition we named the "interval pattern". In 3 subjects no barium left the stomach between the first and second roentgenograms and in 2 subjects the amount of barium in the duodenum made it impossible to decide whether the "interval pattern" was present or not. In 47 subjects the "interval

FIG. 3. The premotion film (64R[1]) illustrates poor gastric tone, peristalsis present and no evidence of pylorospasm. The subject went the full 20 minutes on the motion testing device and was not made "sick". The postmotion film (64R[2]) shows slight increase in gastric tone, no change in peristalsis, no evidence of pylorospasm but illustrates the "interval pattern". Barium can be seen in the duodenal cap but none appears in the remainder of the duodenum and proximal jejunum.

TABLE 6

The incidence of interval patterns in 100 subjects after being subjected to the motion test

	"IMMUNE" SUBJECTS		"SICK" SUBJECTS		TOTAL	
	No	%	No	%	No	%
Interval pattern	35	52	12	43	47	49
No interval pattern	32	48	16	57	48	51
Total	67	100	28	100	95*	100

* 2 questionable cases and 3 cases where interval pattern could not occur omitted

pattern" was noted; in 48 it was definitely not present and in 5 it was impossible to decide.

Table 6 shows the distribution of the "interval pattern" in the "sick" and "immune" subjects. Among the "immune" subjects the "interval pattern" was present in 52% and absent in 48%. Among the "sick" subjects it was present in 43% and absent in 57%. These differences are not significant and there is apparently no relationship between the occurrence of an "interval pattern" and "sickness" or "immunity" on the motion test.

DISCUSSION

A search of the literature fails to reveal any reports related to the study of gastro-intestinal activity of subjects exposed to experimentally induced motion. Campbell (2) in discussing airsickness refers to the effect of stimuli on the gastro-intestinal tract secondary to testing in a mechanical device for producing motion. He presents roentgenograms of two subjects so tested; one who became motion "sick" and the other "immune". The two subjects on whom Campbell's roentgenograms were taken are included in this report as they were members of this series of 100 subjects studied.

The data already presented in this study allow three possibilities to be discussed. First, does experimentally induced motion, which in susceptible individuals produces motion sickness, have any effect on the motor activity of the stomach and small bowel of the subjects who were "immune" to this type of motion? The observations on gastric tone and peristalsis, pylorospasm and intestinal progress of the barium meal as studied roentgenologically show that in both the "sick" and "immune" subjects both gastric tone and peristalsis could increase or decrease, pylorospasm could disappear or develop and intestinal progress could change from less than normal to normal. In the "immune" subjects, however, the general rule was that stomach and small bowel motor activity continued throughout motion testing without appreciable change. The few "immune" subjects in which changes in gastric tone, peristalsis and pylorospasm occurred probably would have shown these same changes during this time interval whether they spent it on the motion testing device or pursuing their usual activities. One exception was the occurrence of the "interval pattern" which was noted in approximately half of all subjects tested. The presence of this "interval pattern" after testing apparently had no relation to motion "sickness" as it occurred with almost equal frequency in both the "immune" and "sick" subjects. To our knowledge this picture has not been described previously under these conditions. Apparently an interval occurs in these subjects, while being motion tested, during which no barium leaves the stomach with intestinal activity at or about the same time emptying the duodenum and proximal jejunum. The presence of pylorospasm would best explain the failure of barium to leave the stomach during testing in these subjects showing the "interval pattern" but this could not be demonstrated in all cases because in many barium was seen in the duodenal cap although no barium was noted in the remainder of the duodenum or proximal jejunum. Of course, there is the possibility that pylorospasm was present during testing, which prevented the barium from leaving the stomach, and that during the time (3 to 4 minutes) it took the subject to go from the motion testing device to the x-ray room the pylorus relaxed and pylorospasm was no

longer present at the time the roentgenographic or fluoroscopic studies were made.

Another possible explanation for this phenomenon is that spastic contraction of the duodenum beyond the cap and of the proximal jejunum occurred, thus emptying the barium from this part of the small bowel caudad and allowing no more to enter. Ingelfinger and Moss (3) have demonstrated by the balloon method that nausea produced by either labyrinthine excitation or after the administration of morphine sulphate results in a generalized contraction of the descending duodenum. They conclude, "It is suggested that duodenal spasm is a frequent concomitant of nausea and that this spasm pushes the duodenal contents into the stomach by reversing the intestinal gradient. Necessarily, absolute pylorospasm during nausea would be impossible". This mechanism would explain why the "interval pattern" was found independent of pylorospasm but the fact remains that the "interval pattern" was found with equal frequency in both the motion "sick" and "immune" subjects. Nausea may have produced a generalized contraction of the duodenum, which in turn resulted in the "interval pattern" in the "sick" subjects but this fails to explain the same results noted in the "immune" subjects who were never nauseated.

Spiegel and Demetriedes (4) also demonstrated a contraction of the intestine in dogs when the external auditory meatus was stimulated with warm or cold water. They did not state what relationship the results bore to the presence or absence of nausea.

Mackie and Pound (5) have described "pocketing" of an opaque meal in the distal ileum with cessation of gastric peristalsis and absence of barium in the duodenum, but their findings occurred in cases with dietary deficiencies in which motion played no part. Barclay (6) describes what may be a similar picture when he states, "In nearly all these cases I found at seven hours there was a complete gap between food in the stomach and that which was collected in a mass behind the ileo-cecal valve. All the cases submitted to operation showed definite evidence of old inflammatory changes in the ileo-cecal region". There is not the slightest evidence that any of our subjects were suffering from a dietary deficiency or "inflammatory changes in the ileo-cecal region".

Whatever the mechanism behind the production of the "interval pattern", it apparently occurs secondary to motion and can be called an effect of motion. It bears no relationship to whether the subject becomes "sick" or remains "immune". Why it occurred in only about one-half of the subjects remains unexplained.

The second possibility for discussion is concerned with whether the roentgenographic appearance of the stomach and small bowel differs in those who become "sick" or those who are found to be "immune" when subjected to

intestinal series revealed a surprisingly high percentage of abnormalities. In the total group examined by this method, 11, or 50 per cent, had abnormal barium series. This consisted of either marked pyloric or duodenal spasm or prominent and pathological hypertrophy of the gastric rugae with some hypersecretion. In two cases both were encountered". Schwab's findings probably represent the results of prolonged gastro-intestinal disturbances secondary to the repeated nausea and vomiting associated with the seasickness for which his patients were hospitalized and it cannot be inferred that these patients were susceptible to seasickness because of the gastro-intestinal abnormalities he describes. Certainly the 28 subjects in our series who became motion sick on the testing device differed not at all in their pre-testing gastro-intestinal findings from the 72 subjects who were "immune" when tested. In addition one of us (M. S.) has, by routine gastro-intestinal barium studies examined 50 aviation cadets or air crew members who were hospitalized for study because of repeated disabling airsickness. In this group he was unable to find any greater variations from normal than is found in individuals of a comparative age and sex group. Most of these 50 patients were subsequently eliminated from further air crew training, or duties involving flying, because of their marked susceptibility to airsickness.

Careful gastro-intestinal histories taken by one of us (F. McD.) on 65 navigation cadets, who were in the process of being eliminated from further navigation training because of repeated disabling airsickness, failed to reveal any symptoms suggestive of functional gastrointestinal disorders except in a few subjects. Certainly no characteristic gastro-intestinal history was obtained in the case of these airsick susceptibles that could possibly be interpreted to suggest that functional gastro-intestinal disorders in any way contribute to motion sickness susceptibility. We must conclude, therefore, that there is no specific type of gastro-intestinal tract, either from an anatomic or functional standpoint, which is associated with motion sickness susceptibility.

SUMMARY

1. A roentgenographic study of the stomach and small intestine before and after a motion test is described.

2. The study was made on a group of 100 subjects and the results are presented, analyzed and discussed.

3. A definite decrease in gastric tone and peristalsis occurred after the motion test in a significant number of subjects.

4. Changes in gastric tone and in peristalsis show a statistically significant positive correlation.

5. An "interval pattern" was observed and is described. A possible explanation for its cause is offered. It has not been described previously.

REFERENCES

1. McEachern, D., Morton, G., and Lehman, P.: War Med., 2: 410, 1942.
2. Campbell, P. A.: J. Aviation Med., 14: 126, 1943.
3. Ingelfinger, F. J., and Moss, R. E.: Am. J. Physiol., 136: 561, 1942.
4. Spiegel, E. A., and Demetriedes, T. D.: Monatschr. f. Ohrenh., 58: 63, 1924.
5. Mackie, T. T., and Pound, R. E.: J. A. M. A., 104: 613, 1935.
6. Barcley, A. E.: Brit. J. Surg., 2: 638, 1915.
7. Schwab, R. S.: U. S. Nav. M. Bull., 40: 923, 1942.

TABLE 2

Duration (minutes) of motor inhibition of the gastro-intestinal tract by spasmolytic drugs

Experiments on anesthetized dogs

EXPT. NO.	COMPOUND	I.V.	TYPE OF MOTILITY	GALLBLADDER (STOMACH)	JEJUNUM	COLON (ILEUM)
		mg./kg.				
3	Atropine	0.0004	Spontaneous	(St. increase 11)	0	
5	Atropine	0.014	Spontaneous	15	19	52
6	Atropine	0.02	Eserine-stimulated	0	0	0
5	Papaverine	0.11	Spontaneous	0	0	0
13	Papaverine	0.36	Ac. chol. stimulated	2	5	10
7	Papaverine	0.09	Eserine-stimulated	0	0	0
7	Papaverine	0.22	Eserine-stimulated	0	0	14
9	Papaverine	0.38	Eserine-stimulated	0	0	0
5	Trasentine 6H	0.11	Spontaneous	29	0	7
5	Trasentine 6H	0.28	Spontaneous	14	12	10
4	Trasentine 6H	0.33	Spontaneous	0	0	16
3	Trasentine 6H	0.38	Spontaneous	(St. 22)	32	
1	Trasentine 6H	0.71	Spontaneous			(ileum 33)
4	Trasentine 6H	1.2	Spontaneous	60	0	28
2	Trasentine 6H	2.9	Spontaneous	60	30	>60
12	Trasentine 6H	0.11	Ac. chol. stimulated	11		
12	Trasentine 6H	0.26	Ac. chol. stimulated	15		
10	Trasentine 6H	0.31	Ac. chol. stimulated	28 (St. 27)		45
13	Trasentine 6H	0.36	Ac. chol. stimulated	60	60	60
11	Trasentine 6H	0.63	Ac. chol. stimulated	(St. 90)	110	75
7	Trasentine 6H	0.22	Eserine-stimulated	14	20	55
6	Trasentine 6H	0.33	Eserine-stimulated	60	50	90
8	Trasentine 6H	0.33	Eserine-stimulated	30	29	42
8	Trasentine 6H	0.38	Eserine-stimulated	15	>30	45
9	Trasentine 6H	0.38	Eserine-stimulated	30	30	45
7	Trasentine 6H	0.87	Eserine-stimulated	120	60	105
14	Trasentine 6H	0.57	Barium stimulated		13	9
15	Trasentine 6H	1.6	Barium stimulated	55	65	60
5	Trasentine	0.11	Spontaneous	0	0	0
3	Trasentine	0.28	Spontaneous	0	0	0
4	Trasentine	0.33	Spontaneous	0	0	0
3	Trasentine	0.38	Spontaneous	(St. 0)	0	
1	Trasentine	0.71	Spontaneous			(ileum 0)
4	Trasentine	1.2	Spontaneous	0	0	17
2	Trasentine	2.9	Spontaneous	0	17	23
12	Trasentine	0.11	Ac. chol. stimulated	0		
12	Trasentine	0.16	Ac. chol. stimulated	0		
12	Trasentine	0.26	Ac. chol. stimulated	0		
10	Trasentine	0.31	Ac. chol. stimulated	0 (St. 0)		32
13	Trasentine	0.36	Ac. chol. stimulated	0	15	15
6	Trasentine	0.33	Eserine-stimulated	21	19	13
8	Trasentine	0.33	Eserine-stimulated	17	11	14
15	Trasentine	0.33	Barium stimulated	0	0	0

Ether anesthesia in experiments no. 9 and 13, intravenous nembutal in the rest.

TABLE 2—*Continued*

EXPT. NO.	COMPOUND	I.V.	TYPE OF MOTILITY	GALLBLADDER (STOMACH)	JEJUNUM	COLON (ILEUM)
		mg./kg.				
5	Syntropan	0.11	Spontaneous	0	3	0
13	Syntropan	0.33	Ac. chol. stimulated	0	10	10
9	Syntropan	0.38	Eserine-stimulated		>10	>10
5	DL 219	0.11	Spontaneous	2	0	0
5	DL 219	0.28	Spontaneous	0	0	0
8	DL 219	0.33	Eserine-stimulated	increase 15	14	43
9	DL 219	0.38	Eserine-stimulated	0	0	0
5	Cyverine	0.11	Spontaneous	0	0	0
5	Cyverine	0.38	Spontaneous	0	0	0
9	Cyverine	0.38	Eserine-stimulated	10	0	0

mg. p. kg. of Trasentine 6H respectively produced a prolonged decrease in tone and motility.

Jejunum. During spontaneous activity, papaverine, Syntropan, DL 219, and Cyverine, were without significant effect. 0.014 mg. p. kg. of atropine inhibited, and doses of 0.28 mg. and above p. kg. of Trasentine 6H were effective in half of the tests. Spontaneous motility of the jejunum (ileum and colon behaved likewise) apparently is less affected by spasmolytic drugs than the motility excited by artificial parasympathetic stimulation.

When jejunal motility was stimulated by acetylcholine or eserine, 0.02 mg. p. kg. of atropine was without effect. Papaverine had little or no effect, as might be expected. In the case of atropine, larger doses undoubtedly would have depressed motility, but were not used since we desired to remain within the range of non-toxic, comparable doses. Trasentine 6H had a constant and considerable spasmolytic effect; that of Trasentine was constant, but of much shorter duration. Syntropan inhibited the jejunum for short periods of time. DL 219 had an inconstant, and Cyverine had no effect.

Colon. In all experiments with comparable doses of effective spasmolytic drugs the periods of inhibition of the colon were longer than those of the stomach or jejunum. The spontaneous motility of the colon was affected more readily than that of the jejunum. In general, the effectiveness of the various spasmolytic drugs on the colon and on the ileum were similar.

Gallbladder. The drugs which markedly decreased spontaneous and artificially stimulated motility and tone of the organ, were atropine and Trasentine 6H. DL 219 was followed by an increase of gallbladder activity, and Cyverine had a short spasmolytic effect on the stimulated organ. Papaverine in doses from 0.09–0.38 mg. and Trasentine in doses from 0.11–2.9 mg. p. kg. was ineffective.

Blood pressure and respiration were recorded, but the results were not in-

cluded in Table 2. In the experiments with spontaneous motility, small and medium doses of each drug caused either no or only small and transient changes in blood pressure. When acetylcholine was given by continuous injection, the administration of Trasentine 6H and of Trasentine were followed by a significant and often prolonged rise in blood pressure in a number of experiments, such as is known to occur with atropine. The effects of the spasmolytic drugs on respiration were slight and evanescent.

Sphincter of Oddi and duodenum. In connection with other work the effect of a number of antispasmodics on the extrahepatic biliary system was studied in the dog (5, 6). Atropine 0.2–0.3 mg. intravenously abolished the tonus rhythm of the sphincter of Oddi and duodenal motility, and decreased the tonus of the gallbladder slightly. Papaverine did not cause uniform changes in the motility of the sphincter or of the duodenum; intravenous doses of 8–15

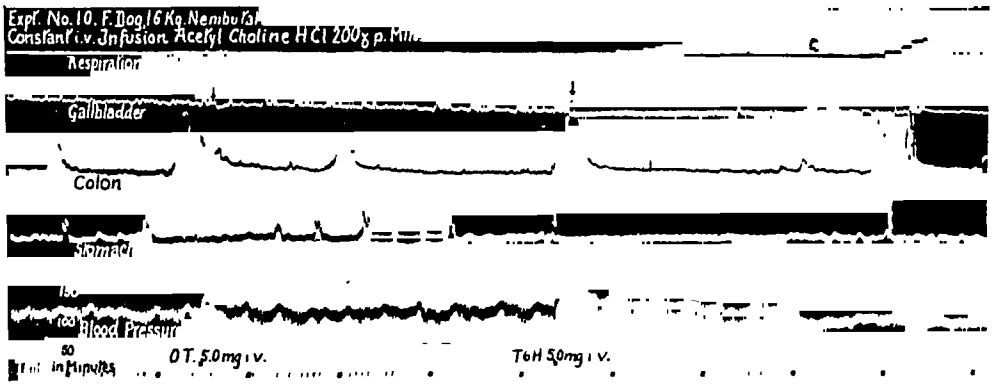


FIG. 1. Effects of trasentine and trasentine 6H on gastro-intestinal motility of the dog stimulated by constant infusion of acetylcholine. 5 mg. of trasentine had little effect. 5 mg. of trasentine 6H depressed motility of gallbladder (28 minutes), stomach (27 minutes) and colon (45 minutes).

mg. were followed in 5 out of 10 tests by an initial relaxation and a secondary rise to or above the control tonus level of the sphincter and duodenum; in the other 5 experiments, spasm of the sphincter and duodenum were the dominant effects. In a few experiments, papaverine was followed by moderate relaxation of the gallbladder; in 2 experiments, the drug produced relaxation of a gallbladder tonically contracted by cholecystokinin.[2]

Trasentine 6H in intravenous doses of 10–25 mg. had effects similar to those of atropine, i.e., the sphincter and duodenum were relaxed markedly, and the tonic contraction of the gallbladder produced by pilocarpine was abolished. Trasentine 6H, like atropine, did not affect appreciably the contraction of the duodenum and of the sphincter following the intravenous infusion of physiological saline solution, the duodenal instillation of gastric juice or egg yolk, or the intravenous injection of cholecystokinin.

[2] Supplied by Dr. D. Klein of Wilson and Co.

The contracting effects of codeine or of prostigmine on the sphincter were reduced or abolished by pretreatment of the animals with either atropine or Trasentine 6H.

Trasentine 6H had a more pronounced relaxing effect on the gallbladder than did comparable dosages of atropine. The relaxing effect of Trasentine on the sphincter of Oddi seemed to be stronger than that of Trasentine 6H.

The effects of DL 219 on the sphincter of Oddi were inconstant, relaxing it in some and contracting it in other tests.

SECRETION. *Salivary secretion in the anesthetized dog.* Salivary secretion of the submaxillary gland was stimulated by pilocarpine or by faradic stimulation. It is seen from Table 3 that atropine depressed secretion in the usual way. Trasentine 6H, in doses comparable to those of atropine, diminished secretion considerably more than atropine. Trasentine (comparable to the doses of atropine and of Trasentine 6H, which were within the range of the average human doses of these drugs) affected secretion much less than Trasentine 6H. Syntropan apparently had the least effect on salivary secretion.

Pancreatic secretion in the anesthetized dog. Trasentine 6H (10 mg. intravenously) had a slight and transient depressing effect on the secretin-stimulated secretion of the pancreas.

Gastric secretion in the unanesthetized dog (Pavlov pouch). Large doses of Trasentine (40 and 50 mg. intravenously) depressed the volume and acidity of the pouch secretion slightly.

Trasentine 6H in doses of 10 mg. (i.v.) had a distinct effect on secretion; free acid was reduced 16% and fluid secretion nearly 50%. A dose of 10 mg. of Trasentine 6H is comparable to an intravenous human dose of 30 mg. Doses of Trasentine 6H below 10 mg. (i.v.) had no appreciable effect on acid secretion, but had an atropine-like depressing effect on the volume of secretion. Twenty mg. of Trasentine 6H (i.v.) reduced free and total acidity from 133/148[3] to 85/111 and the volume (30 minutes) from 21 to 3 cc. Forty mg. of Trasentine 6H (i.v.) reduced acidity from 137/160 to 0/34 and fluid secretion from 30 cc. to 6 cc. This depressing effect of Trasentine 6H lasted for 1.5 to 3.5 hours after the injection of the drug. Rectal temperatures, known to be increased with large doses of atropine, were not affected. Injection of Trasentine 6H depressed fluid and acid secretion much more than atropine in non-toxic doses.

Blood esterase. Suitable doses of Trasentine 6H and Trasentine were found to suppress the vasodepressor effect of small intravenous doses of acetylcholine. Using a method described previously (12), it was found that this was not due to a change of activity of the blood esterase, but to the atropine-like blocking effect of the drugs, which presumably prevents the acetylcholine from entering the effector cells.

[3] Cc. N/10 HCl per 100 cc. of gastric juice.

TABLE 3

The effect of antispasmodic drugs on the salivary secretion of anesthetized dogs

EXPT. NO.	DOG WEIGHT	STIMULATION OF SALIVATION BY (MG. I.V.)	ANTISPASMODIC DRUG, I.V. INJECTION		NUMBER OF DROPS OF SECRETION IN 15 MINUTES
	kg.			*mg*	
1	20	Pilocarpine (0.5)			68
		Pilocarpine (0.5)	Trasentine	5.0	53
		Pilocarpine (0.5)	Trasentine 6H	5.0	15
		Pilocarpine (0.5)	Syntropan	5.0	63
		Pilocarpine (0.5)	Syntropan	20.0	49
		Pilocarpine (0.5)	Atropine	0.00005	36
		Pilocarpine (0.5)	Atropine	0.0001	8
2	15	Pilocarpine (0.5)			25
		Pilocarpine (0.5)	Trasentine 6H	5.0	5
3	15	Pilocarpine (1.0)			84
		Pilocarpine (1.0)	Trasentine 6H	5.0	28
		Pilocarpine (1.0)	Trasentine	5.0	49
		Pilocarpine (1.0)			61
		Pilocarpine (1.0)	Trasentine 6H	5.0	13
		Pilocarpine (1.0)	Syntropan	35.0	13
		Pilocarpine (1.0)	Atropine	0.00005	25
		Pilocarpine (1.0)	Trasentine 6H	5.0	9
4	20	Pilocarpine (0.5)			51
		Pilocarpine (0.5)	Trasentine	5.0	50
		Pilocarpine (0.5)	Trasentine 6H	5.0	15
		Pilocarpine (0.5)	Syntropan	1.0	65
		Pilocarpine (0.5)	Syntropan	5.0	60
		Pilocarpine (0.5)	Syntropan	20.0	48
		Pilocarpine (0.5)	Atropine	0.00005	36
		Pilocarpine (0.5)	Trasentine 6H	5.0	25
5	15	Constant injection pilocarpine 0.00006 per minute			45
			Trasentine	2.0	39
					44
			Trasentine 6H	2.0	13
6	12	Pilocarpine (2.0 s.c.)	Trasentine	5.0	43
		Pilocarpine (2.0 s.c.)	Trasentine 6H	5.0	28
7	12	Pilocarpine (2.0 s.c.) every 45 minutes			50
			Trasentine	5.0	44
			Trasentine 6H	5.0	15
			Trasentine 6H	5.0	29
8	12	Faradic stimulation of chorda tympani			*drops per minute*
			Trasentine	5.0	8
					7-5-6-5-5
					8
			Trasentine 6H	5.0	8-5-5-4-2-1

Surface anesthetic effect. Trasentine, Trasentine 6H and other related compounds are known to have topical anesthetic action (13). Gillman and his colleagues (14) have stated that the local anesthetic potency of Trasentine in block and surface anesthesia is greater than that of cocaine.

In acute and chronic experiments on dogs, we have found recently that the topical, surface anesthetic action of Trasentine and Trasentine 6H produced a greater relaxation of normal or distended segments of the small or large intestines, than that which followed their intravenous injection or their introduction into a loop of intestines distal to the recording balloon (15). Trasentine seemed to be decidedly more effective than Trasentine 6H. Of a number of other drugs studied (procaine, pontocaine, methycaine, butyne, etc.), procaine was the most promising in this regard.

The latent period for relaxation of the gut following the topical application of Trasentine is longer than that following its intravenous injection. Whether this is due to local anesthesia of sensory receptors and interruption of local reflex arcs, or due to an infiltration and anesthesia of the muscular autonomic plexus, remains to be seen. The latter alternative is improbable, however, because on its way through the mucosa, submucosa and part of the muscularis to Meissner's plexus, most of the drug would be absorbed by the blood and lymph and its final concentration at the plexus would be too low.

DISCUSSION AND CONCLUSIONS

The spasmolytic drugs are usually classified into three groups: those which relax smooth muscle directly (papaverine-like effect), those which relax smooth muscle by blocking motor impulses from entering the effector cells (atropine-like effect), and those which have a mixed effect (papaverine + atropine-like effect). This classification is based chiefly on *in vitro* experiments with isolated organs. It is felt that *in vivo* experiments, particularly in unanesthetized animals and on the human subject, yield results which provide a better estimate of the therapeutic value of drugs. We have found recently in the dog and in man that prostigmine has some direct muscular effects, which are not abolished by doses of atropine sufficient to suppress the vasodepressor effect of acetylcholine completely (16, 17). Therefore, the above classification of spasmolytic drugs, cannot be used strictly and is of no great value in clinical therapeusis.

Two of the spasmolytic drugs which were found in the above tests to be quite effective, namely Trasentine and Trasentine 6H, had distinct antispasmodic action on the smooth muscle directly (see Table 2, barium experiments), and indirectly through blockage of motor impulses to the smooth muscle. This confirms our previous results with Trasentine (3) and those of Meyer and Hoffman (13), Graham and Lazarus (7) and Lehman and Knoefel (18, 19).

Syntropan has been shown by the latter authors to have no papaverine like effect (19); other authors have claimed the contrary, however (20).

The recent experiments by Crohn and his colleagues (15) have shed new light on the mode of action of Trasentine. The topical anesthetic effects of the drug may be more important than its systemic effects under conditions of adequate local concentration. It was proposed to instill Trasentine through the Miller Abbott tube in selected cases of ileus prior to surgery, and to employ a solution of the drug in cases of cardiospasm (21).

The most effective drugs studied in this investigation were atropine, Trasentine and Trasentine 6H. Trasentine and Trasentine 6H have been reported to have less disturbing side effects than atropine, such as mydriasis, dryness of the mouth, and increase of heart rate (1, 4, 7, 13, and others). Of the two drugs, Trasentine has less side effects than Trasentine 6H. The greater retardation of gastric motility by Trasentine 6H may be objectionable in certain diseases (peptic ulcer) and beneficial in other ones (achlorhydria and certain types of diarrhea).

We conclude that Trasentine and Trasentine 6H are drugs with important therapeutic aspects, and that only a clinical trial would determine which of the two is preferable.

Toxicity of Trasentine and Trasentine 6H. The above results encouraged us to undertake a clinical study of Trasentine 6H, the results of which could be compared with those of a similar previous investigation of Trasentine (4). It was necessary, of course, to ascertain the safety of the drug and its therapeutic dose. The toxicity of Trasentine 6H has been studied by Meyer and Hoffman (13), Graham and Lazarus (7), and Reynolds (22). Although the data of the various investigators vary to a great extent, they indicate that the L.D. 50 is more than 50 times greater than the amounts which, in our experiments, had a distinct spasmolytic effect. We have administered large doses of Trasentine 6H (from 100 to 400 mg. per kg.) intramuscularly to six dogs in order to ascertain the toxic symptoms of the drug. One dog received 400 mg. p. kg. twice in 2 days. None of the 6 animals died. The characteristic toxic symptoms were weakness, defecation and urination. Vomiting occurred with doses of 125 mg. p. kg. and above, and convulsions were observed with doses of 250 mg. p. kg. and above. Despite the serious symptoms, all animals appeared normal the next morning. One of the animals (400 mg. p. kg.) was sacrificed a week later; histological studies revealed no changes. A rather interesting observation was made when two of the dogs used in the above toxicity tests were anesthetized with sodium pentobarbital a few days later. Both animals were found to be distinctly more susceptible to relatively small doses of nembutal than normal dogs.

CLINICAL EXPERIMENTS AND THERAPEUTIC RESULTS

Effect of spasmolytic drugs on the resistance of the sphincter of Oddi. Ten cholecystectomized patients with a T tube drain in the common duct were used. All were in good condition, without clinical or subjective symptoms, with normal temperatures shortly before the drain was to be removed. The resistance of their sphincter of Oddi to perfusion with saline was recorded by a method previously described (2, 5, 6) and the effect of the various spasmolytic drugs was observed. The results have been reported in connection with another investigation (5, 6) and will therefore be stated only briefly here.

Atropine sulfate. One one-hundredth grain injected subcutaneously in two patients was followed by increased resistance of the sphincter, and was accompanied by vertigo, sinking feeling, blurred vision, dry tongue, and mydriasis. The increased resistance of the sphincter may have been due rather to discomfort and spasm of the sphincter than to atropine (5). Bergh and others have reported that atropine had no effect on the sphincter (23).

Opium. One-half of a grain, and *belladonna* 0.25 of a grain, in a suppository was followed 10 minutes later by a considerable increase in sphincteric resistance which then fell below control levels. For the following 2 hours waves of contraction and relaxation of the sphincter were observed.

Papaverine HCl. Thirty and 50 mg. subcutaneously or intramuscularly, respectively, were given to two patients. In one, a prolonged increase in sphincteric resistance occurred. In the other patient, sphincteric resistance increased for 10 minutes and, 30 minutes later, fell to low levels.

Cyverine. Twenty mg. orally was followed by a moderate increase in sphincteric resistance lasting for 10 minutes.

DL 219. Twenty-five mg. intramuscularly was followed in one patient by a considerable decrease in sphincteric resistance thirty minutes after injection which lasted 15 minutes.

Amyl nitrite was given by inhalation. In one patient, a slight and in another one, a considerable increase in sphincteric resistance occurred. In 2 patients, in whom sphincteric resistance was greatly elevated following codeine or morphine, a sharp transitory decrease of resistance occurred, but the relief of spasm was rarely more than 5 minutes in duration.

Nitroglycerin. One one-hundredth grain orally, administered after codeine or morphine, lowered sphincteric resistance regularly in 3 subjects for periods varying from 5 minutes to hours.

Oil of peppermint or peppermint water, which has been used as a carminative and antispasmodic for a long time (24, 25), had inconsistent effects on the sphincter (oral administration). Tincture of valeriana, citric acid, and a watery solution of oil of spearmint had slight or no effects on the sphincter.

Trasentine and Trasentine 6H were administered to 4 patients subcutaneously or intramuscularly in doses varying between 25 and 75 mg. The administration of Trasentine was followed by a decrease in sphincteric resistance, while Trasentine 6H had only a slight or no effect. In 3 patients Trasentine 6H was employed before or after a spasm of the sphincter had been produced by codeine. The spasm was reduced considerably in both cases. Atropine sulfate 1/150 gr. subcutaneously had similar effects. In these experiments the subcutaneous or intramuscular administration of 25 mg. of Trasentine 6H was not followed by side effects, but larger doses caused dryness of the mouth. Injections of Trasentine had no such effects. Trasentine 6H, Trasentine and atropine were more effective in preventing or diminishing spasm produced by drugs than in lowering the natural tonus of the sphincter. This was observed in experiments on man as well as on dogs (v.s.).

Clinical results. Thirty-eight patients who had been studied for months or years were submitted to treatment with Trasentine 6H. Most of the cases were chosen because previous routine therapy[4] had not been entirely satisfactory. All patients were continued on diets which had been instituted previously, according to clinical routine. They received one 50 mg. tablet of Trasentine 6H three times a day per os, except where otherwise stated.

The first group consisted of 17 patients suffering from duodenal ulcer; the diagnosis was verified in 15 by x-ray; in two, the x-ray diagnosis was questionable, but the clinical impression was distinctly that of duodenal ulcer. Five of these patients received Trasentine 6H in combination with aluminum hydroxide cream. Three of them obtained complete relief from all symptoms, while previous therapy had been ineffectual. Another patient had less relief with aluminum hydroxide plus Trasentine 6H, than with aluminum hydroxide alone. In another patient the combination of both drugs was superior to previous therapy, but did not afford complete relief of symptoms. The combination of Trasentine 6H and aluminum hydroxide was more effective in 3 patients than either medication alone. In one patient complete relief from symptoms was obtained either with atropine or with Trasentine 6H.

The second group consisted of 6 patients, suffering from gastric or gastrojejunal ulcers, the latter following gastroenterostomies or subtotal gastric resection. Their response to Trasentine 6H was not dramatic, although in 4 out of 7 cases it was superior to previous routine therapy. One patient, who responded particularly well, had a relapse 4 weeks later, although still under Trasentine 6H medication.

The third group consisted of 3 cases of gastritis, in all of whom Trasentine 6H was of no benefit.

The fourth group comprised 4 patients with biliary tract symptoms. In

[4] Routine therapy consisted of the administration of sedatives, atropine or belladonna, antacids, mineral oil, diet, etc.

only one of these, suffering from biliary dyskinesia following cholecystectomy performed 5 years ago, was complete relief obtained with Trasentine 6H from attacks of right upper quadrant pain, nausea, belching, and, at times, slight icterus, usually following dietary indiscretions. The patient has taken Trasentine 6H on and off for the last two years. Belladonna and sodium bicarbonate did not give relief.

The observations on 3 patients with ulcerative colitis were of interest and merit a more detailed description of the two of the cases.

One patient with a severe ulcerative colitis was treated in the hospital with diet, opiates, sedatives, blood transfusions, etc., with little effect on the bloody diarrhea and pain. The intravenous administration of 50 mg of Trasentine 6H reduced the number of stools, the abdominal pain and tenesmus. The intravenous medication had to be abandoned, however, because the side reactions were too disturbing. Trasentine 6H was given by mouth, and the number of stools per day was reduced from 20–25 to 3–4. The administration of 5 tablets a day was still followed by dryness of the mouth and therefore, the dose was reduced to 1 tablet 3 times a day. With this dose, no side reactions occurred, and the stools decreased to 1 to 2 per day and became solid, blood-free and normal in appearance. Since then this patient has taken one tablet every other day and has felt well for months, doing light work or studying. Occasional relapses, due to dietary indiscretions or mental upsets, have occurred, but an increase of the dose to 3 tablets a day restored him every time. He has not been able to live comfortably without taking one tablet of Trasentine 6H every other day. When the drug was omitted for a few days, the number of bowel movements increased. This patient evidently was not cured, but the reduction of the number of stools, the gain in weight and the general condition were gratifying.

In another case of ulcerative colitis with ileostomy the intramuscular injection of 25 mg of Trasentine 6H reduced the flow from the fistula and the abdominal pain and distention. The daily oral administration of 4 tablets of Trasentine 6H had the same effect, but complete relief as in the previous case was not afforded.

Trasentine 6H, per os, abolished the abdominal pain and constipation in one patient with spastic colon, in whom belladonna and sedatives had afforded little relief. In another patient with duodenal ulcer, suffering from subacute non-specific diarrhea, administration of Trasentine 6H abolished the diarrhea and tenesmus.

In a case of gastroptosis and heart burn, relief from heartburn was obtained with two tablets of Trasentine 6H, t.i.d., half an hour before meals.

Side reactions. Dryness of the mouth, headache, dizziness and dilation of the pupils were observed in 7 out of the 41 patients. In two patients the reactions followed parenteral and in the rest oral administration. In another patient, not included in this series, a transient paralysis of the lower extremities was noted, following the intravenous injection of 50 mg. of Trasentine 6H; for obvious reasons, no further injections were given.

Experiments on salivary secretion in the normal human subject. Three of the patients receiving 50 mg. of Trasentine 6H three times a day by mouth, one

patient with an oral dose of 50 mg. 5 times a day, one patient with 50 mg. intravenously 3 times a day, and another with 25 mg. intravenously twice daily, complained of considerable dryness of the mouth. The effect of a single dose of 50 mg. of Trasentine 6H per os was studied, therefore, on the salivary secretion of 4 healthy male subjects 18–26 years of age. Gum was chewed and all saliva was expectorated. After 2 control periods of 30 minutes each, one tablet of 50 mg. of Trasentine 6H was swallowed and, one hour later, saliva was collected for another two, 30 minute periods. The amounts secreted in the controls and in the hour following the ingestion of the drug were as follows 28.5:36.0; 27.5:24.5; 39.3:55.5; 28.2:34.5. Except in one experiment, all subjects had an increased flow of saliva following Trasentine 6H.

DISCUSSION

In general, the therapeutic results obtained in this group of carefully observed patients are such as might have been expected from our animal experiments. In the clinical trials, Trasentine 6H proved to be a fairly good antispasmodic, without yielding, however, a greater number of impressive or convincing effects than one is accustomed to observe with other antispasmodics administered in adequate dosages. In comparing the clinical effects of Trasentine 6H with those noted and described for Trasentine (4), the pharmacologically greater potency of Trasentine 6H seen in the animal experiments was not paralleled by superior clinical effects. The relief the patients obtained was not more striking either in percentages or in degree or speed of abolition of symptoms, than we had observed with Trasentine (4). Furthermore, the incidence of side reactions, 7 in our series of 38 patients, was greater than found earlier with Trasentine (4), and in later clinical use. The repeated complaint of dryness of the mouth and throat may be explained by the results of our dog experiments, where the atropine-like depression of salivary secretion was obvious. The results of our tests on the salivary secretion of 4 normal human subjects were opposed to this. Whether the prevailing conditions in the normal subjects were different from those in the patients, or whether individual sensitivity may have been present in our patients, remains an open question.

Following the intravenous injection of Trasentine 6H, we have also seen a surprising and disturbing reaction which requires further study before it may be explained. The patient suffered from severe malaise and an inability to control and coordinate movements of the lower extremities. This side effect although not serious and lasting only 10 or 15 minutes, indicates caution in the parenteral use of Trasentine 6H.

In the experiments on the resistance of the sphincter of Oddi in the human, Trasentine and nitroglycerine were found superior to atropine, opium-belladonna, papaverine, amylnitrite, Trasentine 6H, DL 219, and Cyverine. It is our opinion therefore, that Trasentine 6H, inspite of its distinct pharmacological effects, does not offer any advantages superior to those of Trasentine.

SUMMARY

A comparative experimental and clinical study was made of some of the well known and of a number of the newer spasmolytic drugs.

The effects of the drugs on salivary, gastric and pancreatic secretion, and on gastric and intestinal motility of the dog were studied.

The effects of the drugs on the salivary secretion of the normal human subject, and on the resistance of the sphincter of Oddi of patients were determined. Finally, the clinical results of the use of one of the drugs, Trasentine 6H, in a group of 38 patients suffering from various gastro-intestinal diseases were observed.

A comparison of the value of the different drugs on gastro-intestinal symptoms showed that atropine and Trasentine and, in spasm of the sphincter of Oddi, Trasentine or nitroglycerine, were most effective. Trasentine yields a smaller incidence of undesirable side reactions than Trasentine 6H. Syntropan had the least effect on salivary secretion.

It is concluded that Trasentine 6H is not as useful clinically as Trasentine.

REFERENCES

1. Jackman, R. J., and Bargen, J. A.: S. G. & O., 67: 63, 1938.
2. Butsch, W. L., McGowan, J. M., and Walters, W.: S. G. & O., 63: 451, 1936.
3. Necheles, H., Neuwelt, F., Steiner, N., and Motel W. A.: Am. J. Dig. Dis., 6: 39, 1939.
4. Spier, E., Neuwelt, F., and Necheles, H.: Am. J. Dig. Dis., 6: 387, 1939.
5. Necheles, H., and Kozoll, D.: Am. J. Dig. Dis., 9: 36, 1942.
6. Kozoll, D., and Necheles, H.: S. G. & O., 74: 961, 1942.
7. Graham, J. D. P., and Lazarus, S.: J. Pharm. & Exper. Therap., 69: 331, 1940.
8. Slaughter, D., Van Duzen, R. E., Johnson, T. U., and Tobolowsky, N.: South. Med. J., J., 35: 541, 1942.
9. Neuwelt, F., Olson, Wm. H., and Necheles, H.: Proc. Soc. Exper. Biol. & Med., 44: 74, 1940.
10. Olson, Wm. H., and Necheles, H.: J. Lab. and Clin. Med., 27: 802, 1942.
11. Necheles, H., and Olson, Wm. H.: J. Lab. and Clin. Med., 26: 1647, 1941.
12. Ginsberg, R., Kohn, R., and Necheles, H.: Am. J. Dig. Dis., 4: 154, 1937.
13. Meier, R., and Hoffmann, K.: Helvetica Med. Acta, Suppl., VI, 7: 106, 1940–41.
14. Gilman, A., Goodman, L., Thomas, J. M., Hahn, G. A., and Prutting, J. M.: J. Pharm. & Exper. Therap., 74: 290, 1942.
15. Crohn, N., Olson, Wm. H., and Necheles, H.: Bull. Am. Coll. Surgeons, 28: 46, 1943.
16. Meyer, J., and Necheles, H.: J. Lab. and Clin. Med., 27: 162, 1941.
17. Schwartz, H., Reingold, I., and Necheles, H.: Surgery, 2: 746, 1942.
18. Lehman, G., and Knoefel, P. K.: J. Pharm. & Exper. Therap., 74: 217, 1942.
19. Lehman, G., and Knoefel, P. K.: J. Pharm. & Exper. Therap., 74: 274, 1942.
20. Fromherz, K.: J. Pharm. & Exper. Therap., 60: 1, 1937.
21. Necheles, H.: The Use of Drugs in Gastro-Intestinal Disorders. Chapter in Tice, Practice of Medicine, Prior Co., In Press.
22. Reynolds, S. R. M.: Unpublished results, personal communication.
23. Bergh, G. S.: Surgery, 11: 299, 1942.
24. Meyer, J., Arens, R., Sapoznik, H., and Necheles, H.: J. A. M. A., 104: 20, 1935.
25. Meyer, J., Scheman, L., and Necheles, H.: Arch. Int. Med., 56: 99, 1935.

THE LIFE CYCLE OF CARCINOMA OF THE STOMACH

Report of Three Interesting Cases of Carcinoma of the Pylorus

Maurice Feldman, M.D.
Baltimore, Maryland

Often one wonders how long a carcinoma has been present before it is recognized. The following three cases are of great interest because they show that either carcinoma or a precarcinomatous lesion was present for a number of years before a definite diagnosis was made.

CASE 1

H. M., male, aged 56, was first seen in 1925 when he complained of intermittent pains in the right abdomen. A gastrointestinal x-ray examination revealed no organic pathology. Cholecystography revealed a normal gall bladder.

In 1927, two years after the onset of symptoms, the gastrointestinal study was negative. However, there was a slight narrowing of the prepylorus, which was not considered abnormal.

In 1931, six years after onset, the gastrointestinal examination yielded negative results, but with a similar prepyloric narrowing.

In 1937, twelve years after onset, gastrointestinal studies revealed a narrowing of the prepyloric end of the stomach which differed from the narrowing noted previously (Fig. 1, lower left). There were also fluoroscopic changes which suggested a duodenal ulceration. For the first time during the many years of repeated gastrointestinal studies, a nine hour gastric retention was found, which was thought to be significant and further studies were advised.

In 1940, fifteen years after onset, he was re-studied with negative findings. Even the gastric retention which was observed in 1937 was absent at this time.

In 1942, seventeen years after the onset of symptoms, gastrointestinal examination revealed a large annular filling defect in the prepylorus with a 24 hour gastric retention. At operation an inoperable carcinoma was found.

Comment: There was a low gastric acidity which had persisted throughout the course of the illness. At no time did the patient have symptoms that would have led to the suspicion of carcinoma until late in the course of the disease. Because of the persistency of the digestive complaint, he was advised to be explored in 1931, six years after the onset of the symptoms. The roentgen examination revealed a prepyloric narrowing many years prior to the time of exploration. At no time was a palpable mass felt until late in the course of the disease. Although the patient had had digestive symptoms for many years, it was not until 1937 that a gastric retention was noted. The narrowing of the prepylorus noted in the earlier examinations was believed then to have

had no clinical significance, but its persistency, in addition to the gastric retention, led us to suspect an organic lesion.

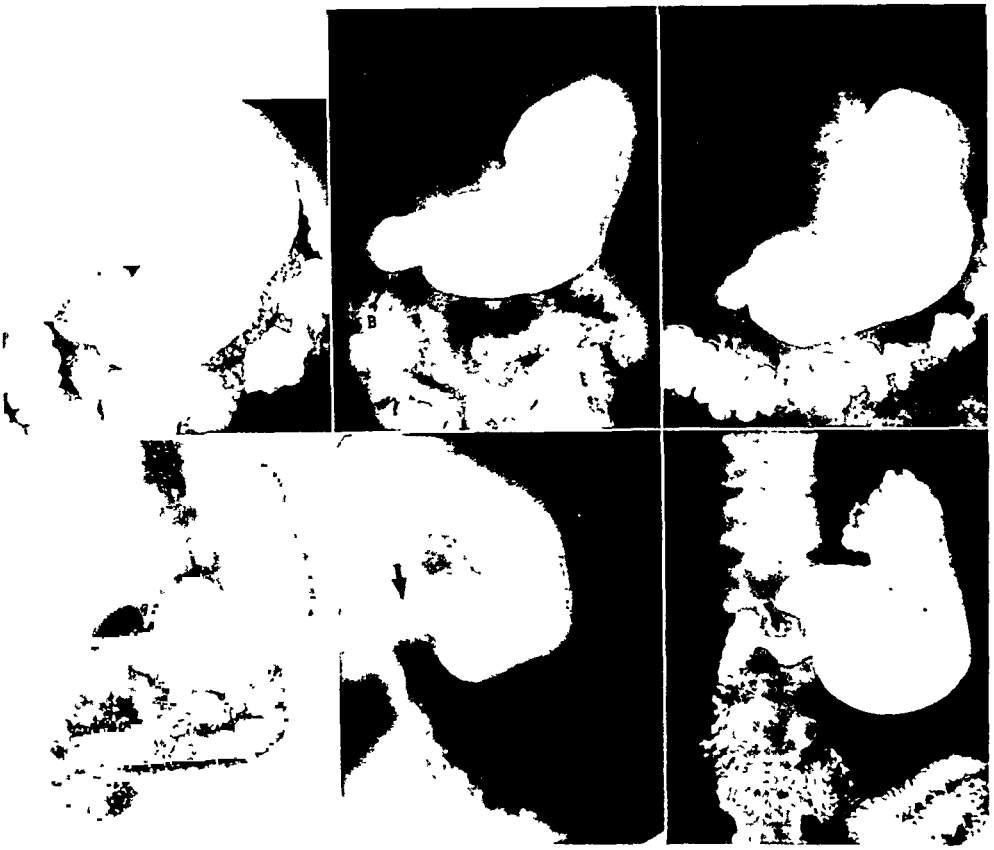


FIG. 1. Case 1. (Upper left.) Roentgenogram made in 1925. The stomach appeared to be normal. The pylorus and duodenal cap are well filled and normal in contour.

(Upper center.) Roentgenogram made in 1927. Note the shallow bulge on the lesser curvature at arrow A. The beginning narrowing of the prepylorus is shown at arrow B.

(Upper right.) Roentgenogram made in 1931. Demonstrates the narrowing of the prepylorus, which is more marked than that noted in 1927.

(Lower left) Roentgenogram made in 1937. Note the smooth narrowing of the prepylorus at arrows, which tapers toward the sphincter This tapering was not seen in the two previous examinations. At this time there was a nine hour gastric retention.

(Lower center.) Roentgenogram made in 1940. An increase in the prepyloric narrowing is shown. Note the smoothness of the curvatures and the plateau appearance at arrow.

(Lower left.) Roentgenogram made in 1942. The large annular defect of the prepylorus is shown.

CASE 2

C. A. G., male, aged 59, in 1938, when he was examined for the first time, complained of epigastric pain immediately after meals, vomiting of blood on one occa-

sion, good appetite and no loss of weight. A gastrointestinal x-ray study revealed a narrowing of the prepylorus, in which the departure from the normal was so slight that one could not interpret it on the basis of an organic lesion. His symptoms were relieved under an ulcer regime.

In 1940, two years after the onset of symptoms, there was a recurrence of the condition. X-ray examination revealed a spastic pylorus and narrowing of the prepylorus, which was thought to be due to a gastritis. There were also signs of a duodenal ulceration. The patient was hospitalized and the symptoms promptly disappeared on conservative treatment.

In 1941, three years after the onset of symptoms, he began to lose weight and strength, vomited blood and the epigastric pain became more intense. Roentgen studies revealed a partial pyloric obstruction with an annular infiltrating ulcerating carcinoma. At operation an inoperable carcinoma was found.

FIG. 2. Case 2. (Left.) Roentgenogram made in 1938. Demonstrates a diffuse prepyloric narrowing, which presented very little departure from the normal.
(Center.) Roentgenogram made in 1940. The diffuse narrowing of the prepylorus is shown with a slightly ragged greater curvature and plateauing of the lesser curvature.
(Left.) Roentgenogram made in 1941. Demonstrates the persistency of the prepyloric narrowing, which is more pronounced than noted in 1938 and 1940.

Comment: This patient's history of digestive complaint extended over a period of three years. Repeated gastric analyses revealed a low acidity. A palpable mass could at no time be felt. In 1940 an exploratory operation was refused. In 1941 the patient was prevailed upon to be operated on for the relief of the obstruction.

CASE 3

H. L., male, aged 73, was admitted to the hospital in 1937. He complained for one year of epigastric pain, becoming worse when hungry—relieved by food and alkalies. He had lost about thirty pounds within a period of six months. There was loss of appetite, belching, distention and constipation. There was no history of vomiting and no evidence of tarry stools. Physical examination was negative. Fractional analysis yielded a hyperacidity. There was occult blood in the gastric

contents. The feces showed a trace of blood in one examination. A gastrointestinal study revealed a persistent narrowing of the pyloric portion of the stomach.

In 1939, two years after the onset of symptoms, an x-ray examination revealed an annular lesion of the pylorus which simulated a carcinoma. There was a small gastric residue.

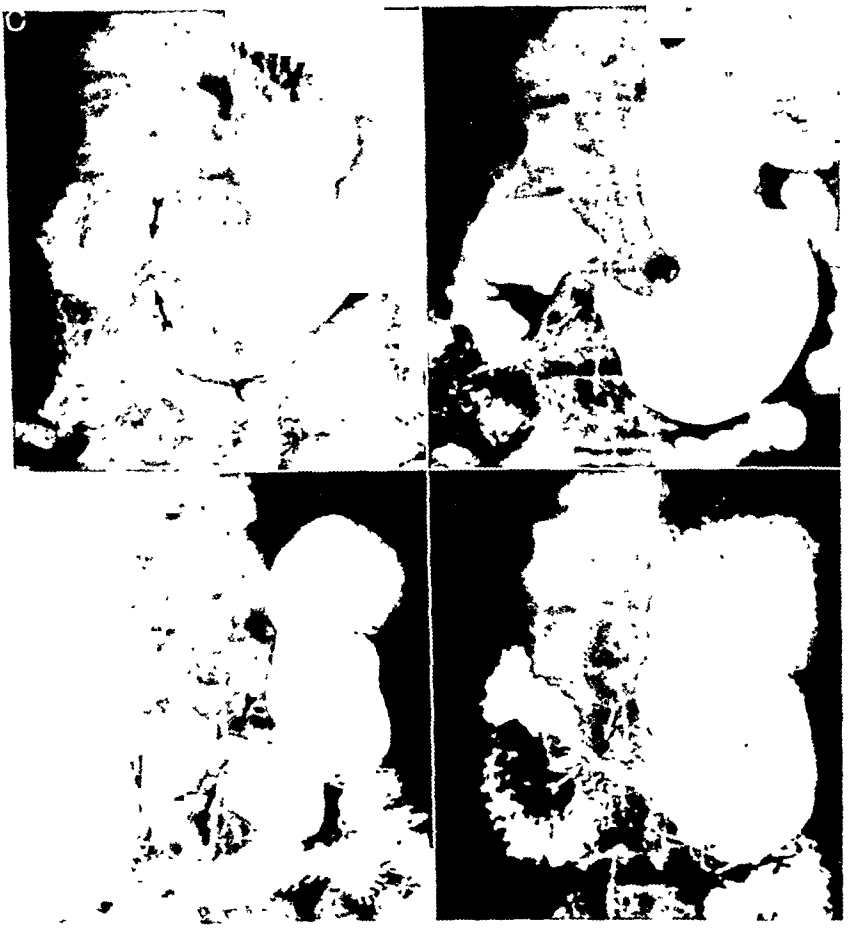


FIG. 3. Case 3. (Upper left) Roentgenogram made in 1937. Narrowing of the prepylorus is shown at arrows.

(Upper right.) Roentgenogram made during the same examination in 1937 shows the changing roentgen picture of the prepylorus

(Lower left.) Roentgenogram made in 1939. Showed the narrowed prepylorus, with a ragged greater curvature, but there was little change from that seen in 1937.

(Lower right) Roentgenogram made in 1943, illustrates the extensive annular carcinomatous defect.

In 1943, six years after his first admission to the hospital, he was re-admitted with a recurrence of symptoms. Fractional analysis again showed a hyperacidity. X-ray studies revealed a pyloric obstruction with an extensive annular infiltrating carcinoma. At operation a large inoperable carcinoma was found.

Comment: Clinically, this patient presented signs of ulceration. There was a persistent hyperacidity. In spite of the fact that the x-ray showed an annular lesion of the pylorus which had the characteristics of carcinoma, he was relieved of symptoms for a period of six years. After each recurrence, roentgen studies were carried out, which showed a progressive narrowing of the prepylorus.

DISCUSSION

These three cases of carcinoma of the stomach closely paralleled each other. They presented the clinical picture of peptic ulceration with periods of remissions. These cases had similar roentgen findings, of narrowing of the prepylorus, involving both curvatures, fixation of the curvatures with a plateau appearance of the lesser curvature in the affected area. They were slow growing carcinomata, extending over many years. Two of the cases had persistent low gastric acidities, while one showed a persistent hyperacidity throughout the entire course of the illness. In all three cases the man finally developed a pyloric obstruction due to an inoperable carcinoma.

Negative roentgenologic information regarding the integrity of the stomach often gives one a sense of false security. The demonstration of a narrowing of the pylorus should lead one to suspect a possible lesion. It is noteworthy to point out that in a patient with a digestive disorder presenting a negative gastrointestinal study, who is clinically progressively getting worse or is not improving, is strongly suggestive of having an organic lesion somewhere in the gastrointestinal tract and repeated interval roentgen studies must be carried out.

The roentgenologist will at times find some changes in the pylorus, such as narrowing and thickening, which should be mentioned, even though the true nature of the condition cannot be definitely established. Clinically, the patient may not manifest symptoms to warrant surgical intervention. Often the surgeon is not courageous enough to explore the stomach because of lack of symptoms when a suspicious organic lesion is demonstrated by the x-ray.

CONCLUSIONS

Three cases are presented which portray an interesting picture of the life cycle of carcinoma of the stomach. Repeated roentgen examinations were made in each case, over a number of years which enabled the writer to study the sequence and progress of the growth from the onset to the final stage.

EDITORIALS

STUDIES ON A NEW ALEXIS ST. MARTIN

Someone once said wisely that often, during the progress of scientific research, two men have looked with great discernment in some one direction, but one learned much more than the other did because, with the passage of years, he had, in a way, ascended a circular staircase, and from his greater height, he could see more. One is reminded of this simile as one reads the delightful and highly instructive book of Wolf and Wolff.[1] Like Beaumont, they looked in a certain direction, but over a hundred years of scientific research had lifted them up so that they knew much better than Beaumont did how to study their human subject and how to get the greatest amount of information from him. Partly because of this, their book is much more useful and interesting than that of Beaumont, good as that is.

Fortunately for them, their subject, Tom, a fifty-seven year old Irishman, was sensitive, worrisome, and decidedly temperamental. He was easily swayed by strong emotions of all kinds, and this helped them in studying the influences of such emotions on the movements and the secretion of the stomach. At the age of nine Tom gulped down some boiling hot clam chowder, and was left with an esophageal stricture and a gastrostomy. A certain amount of gastric mucosa prolapsed and became exposed around the mouth of the fistula. Interestingly, at the beginning Tom suffered with diarrhea and failed to gain in weight until he learned to chew his food before putting it into the stomach. It is hard to guess why this should have happened. Always the man has had a good appetite.

Curiously, although after the taking of a barium meal the stomach emptied in two hours, it did not empty for several hours when he ate ordinary food. The stomach emptied only during periods of vigorous contraction.

The color of the mucous membrane within the stomach as well as without, where it was exposed on the abdominal wall, varied at different times from a faint yellowish pink to an intense cardinal red. When the stomach was quiet and there was little secretion the mucosa was pale; when it was active and there was much secretion of acid the mucosa was red and the blood flow through it was much increased.

The putting into the stomach of pieces of meat, or the mechanical stimulation of the gastric mucosa with a glass rod had no inhibiting effect on the gastric movements, but the introduction of fluids or fats did. This quieting effect came only after the material had reached the duodenum. As was to

[1] *Human Gastric Function.* Oxford University Press, N. Y., 1943—An experimental study of man and his stomach by Stewart Wolf and Harold G. Wolff.

be expected from this, inhibition was prompt when liquids were injected through a tube directly into the duodenum. Evidently, then, in man as in animals, the stomach is inhibited most easily from the duodenum. Swallowing movements, even when nothing was taken into the mouth, caused momentary inhibition of a gastric contraction, if at that time one happened to be running over the stomach.

"Hunger contractions" were often observed, but more than half the time they were not associated with any feeling of hunger. As many observers have shown, at intervals the stomach tends to become more and more active until it gets into a state of almost tetanic contraction.

When smoking was pleasurable to Tom it was not accompanied by any alteration in the pattern of the gastric contractions. Occasionally, however, when he had little taste for smoking and it gave him slight nausea, the gastric waves were inhibited until he felt better again. With nausea there was stoppage not only of gastric contractions but also of acid secretion, and with this there was a marked pallor of the gastric mucosa. At such times there was an increase in the secretion of mucus.

Most interesting was the observation that when Tom's face blushed his gastric mucosa also blushed, and, with this there was a moderate increase in the secretion of acid.

The introduction of 20 cc. of 0.1 N hydrochloric acid into the stomach during a phase of moderately active secretion, for a time inhibited the further production of acid and stimulated the production of mucus.

Atropine in doses of 0.0018 gm. or more inhibited gastric contractions as well as the secretion of mucus and acid. With the stoppage of contractions digestion was delayed for six hours or more. Prostigmine greatly increased both the motor and the secretory activity of the stomach. All research workers should note that emotional states with their profound effects on gastric function could alter greatly the results usually obtained with any drug.

When Tom was discouraged or full of self-reproach the gastric mucosa became pale, and the secretion of acid fell off. When he was angry and resentful, the volume and acidity of the parietal cell output was three times normal, and the mucous membrane was turgid and red. These observations must, of course, be of great interest to every physician who has to treat patients with ulcer. Anxiety also produced hyperemia of the mucosa with hyperacidity, and a sleepless night spent in worrying caused the acidity next morning to be high. Interesting was the fact that when gastric acidity had been increased by some emotional conflict, more than one good night's sleep was needed to bring it back to normal.

Often during the years in which Tom worried much over financial insecurity he suffered from what appeared to be heartburn. This trouble went away as soon as he was assured of a steady income. The symptom could be pro-

duced by injecting into the cardiac end of his stomach irritants such as strong solutions of alcohol, hydrochloric acid or mustard.

It is interesting to note that the physiologic state of the stomach or the appearance of the mucosa did not determine the presence or absence of appetite.

During periods of hyperfunctioning of the stomach, the mucosa often took on the appearance of hypertrophic gastritis. That this was not due to any inflammation was shown by the fact that it would disappear shortly after Tom cooled off emotionally and regained his composure. Anything which caused hyperemia and engorgement of the mucous membrane with hypersection was likely to produce a picture resembling hypertrophic gastritis.

The pinching of the mucosa of the stomach between the blades of a forceps or the application of strong faradic shocks or chemical irritants to the mucosa failed to cause pain. Vigorous pressure on the mucosa did produce a steady, dull, gnawing type of pain, but the impression was that this pain was due to pressure on the muscular or serous coat of the stomach. It was much easier to produce pain by irritating the mucous membrane at a time when it was engorged with blood or edematous, and on a few such occasions severe pain was easily produced. Intense contractions of the stomach sometimes caused nausea.

As can easily be seen, there is much in these observations to throw light on the formation of peptic ulcers and the production of pain by these lesions. As all gastro-enterologists now know, the patient who can get ulcers is usually a man like Tom whose emotions are stormy enough to have markedly stimulating effects on the vascularity of the gastric mucosa, and with this, a marked increase in the secretory activity of the parietal cells.

To us it would seem that the big lesson that patients with ulcer should learn from all this is that they should not wait to start their ulcer diet with frequent feedings and alkalies until they have a flare-up with pain and perhaps a hemorrhage. They should start the treatment the minute they run into the sort of psychic storm which is likely to produce a marked hyperacidity and a new ulcer. They should be particularly careful to keep the gastric acid buffered during the hours between 10 p.m. and 2 a.m. when it would seem that the danger of ulcer formation or deepening is greatest.

WALTER C. ALVAREZ.

ELMER BURKITT FREEMAN

With the death of Dr. Elmer Burkitt Freeman, the Association sustained the loss of a loyal and enthusiastic member.

He was born at Mattoon, Illinois, February 5, 1875, and died December 23, 1942, after a brief illness. Death was caused by coronary disease and cerebral hemorrhage.

Dr. Freeman received his B.S. degree from Austin College in 1896, and his M.D. from the Baltimore Medical College in 1900. In 1903, he was married to Miss Rosa May Weeks, who survives him.

He was Associate Professor of Clinical Medicine of the Baltimore Medical College from 1904 to 1910, and Professor of Therapeutics at the same college from 1910 to 1914. He was visiting physician to the Maryland General Hospital from 1901 to 1917, when he became Physician-in-Chief, and so remained until his death; visiting physician, Bon Secours Hospital, since 1917, and Gastroenterologist, St. Agnes Hospital, since 1910. His teaching positions included Associate Professor of Medicine at the University of Maryland, 1913 and 1914, and Lecturer in Medicine since 1935 at the same institution; Dispensary Physician, Gastrointestinal Department, Johns Hopkins Hospital since 1912; Instructor in Clinical Medicine, Johns Hopkins University, 1922 to 1929; Associate in Clinical Medicine, Johns Hopkins University since 1929; Assistant Visiting Physician at the Johns Hopkins Hospital since 1929.

Dr. Freeman was a member of the Southern Medical Association, and had been both secretary and chairman of the section on Gastroenterology; Fellow of the American Medical Association and Fellow of the American College of Physicians; Diplomat of the American Board of Internal Medicine.

He served on the local Advisory Medical Board during the First World's War, and was serving on Induction Board Number Six at the time of his death.

Dr. Freeman was the author of many articles in the field of Gastroenterology and Internal Medicine. A very large number of his writings were in the field of esophageal disease, in which he was particularly interested. He was especially adept in the use of the esophagoscope, and lately of the flexible gastroscope.

Dr. Freeman enjoyed travel immensely, and was extremely fond of his home, but to say that he had any hobbies would be a distinct error. His life was filled by his work and the short trips he took were usually to attend some medical meeting. His one trip abroad involved attendance at a medical meeting in Paris, France.

His passing is a great loss to his many friends and associates.

HAROLD E. WRIGHT.

A NEW GASTROINTESTINAL HORMONE: PANCREOZYMIN

The apparent discovery of a new gastrointestinal hormone is of interest to gastroenterologists. It should be recalled that some authors trace the beginning of modern endocrinology to the discovery of secretin by Bayliss and Starling (1902); they provided the first systematic proof of the existence of

a hormone and coined the term "hormone." Also, the mucosa of the alimentary tract is a close competitor of the anterior lobe of the hypophysis as a producer of active principles of physiological and clinical interest.

The fact that the external secretion of the pancreas is subject to a dual control, hormonal and nervous, is well established (1). The concentration of enzymes can be uniformly increased by stimulation of the vagi or by the administration of drugs known to stimulate vagal or cholinergic nerve endings (2). It is agreed that secretin increases the amount and the bicarbonate content of pancreatic juice, but the effect of secretin on enzyme output is controversial (1). For example, Lagerlof (3) concludes that "it is unlikely that secretin produces any increased activity within the enzyme-producing cells," and Voegtlin, Greengard and Ivy (4) observed an increase in the total output but not in the concentration of enzymes in their human experiments. Others, have observed an increase in the concentration of enzymes (1, 5, 6).

The variations in enzyme output and concentration observed by different investigators in response to secretin may be due to differences in the method used for making the secretin preparation administered. Harper and Raper (7) have demonstrated this to be true. Using an extract of duodenal mucosa (8), which increased the output of enzymes as well as fluid and bicarbonate, they have prepared a fraction which increased the secretion of enzymes but had no effect on the volume of juice secreted. They have named the active principle "pancreozymin."

The view that "pancreozymin" is of physiological importance is supported by at least two physiological observations. Following the ingestion of food, the autotransplanted pancreas secretes more fluid and enzymes (9). Water in the duodenum increases the output of enzymes in animals with an extrinsically denervated pancreas (10). This means that either secretin increases the secretion of enzymes or the food and water caused the production of secretin and "pancreozymin."

It will be of interest to ascertain whether "pancreozymin" exists in man and the response of the human pancreas to pure secretin and to secretin plus "pancreozymin."

A. C. Ivy.

REFERENCES

1. Thomas, J. E.: Federation Proc., 1: 261, 1942.
2. Comfort, M. W., and Osterberg, A. E.: Am. J. Digest. Dis., 8: 337, 1941.
3. Langerlof, H.: Quart. J. Med., 8 (N.S.): 115, 1939.
4. Voegtlin, W. L., Greengard, H., and Ivy, A. C.: Am. J. Physiol., 110: 198, 1934.
5. Diamond, J. S., Siegel, S. A., Gall, M. B., and Karlen, S.: Am. J. Digest. Dis., 6: 366, 1939.
6. Barrington, E. J. W.: J. Physiol., 100: 39, 1941.
7. Harper, A. A., and Raper, H. S.: J. Physiol., 102: 115, 1943.
8. Greengard H., and Ivy, A. C.: Am. J. Physiol., 124: 427, 1938.
9. Farrell, J. I., and Ivy, A. C.: Am. J. Physiol., 78: 325, 1926.
10. Harper, A. A., and Vass, C. C. N.: J. Physiol., 99: 415, 1941.

BOOK REVIEWS

ALLERGY, ANAPHYLAXIS, AND IMMUNOTHERAPY. *Bret. Ratner, M.D.* $8.50. Williams & Wilkins Co., Baltimore.

Every good allergist must always feel a desire to know as much as possible about the scientific principles underlying his specialty. Only with such knowledge can he think independently and constructively. This book was written to give up-to-date information about such things as the anatomy and physiology of the minute vessels of the skin, the mechanism which produces eosinophilia, the RH factor in the blood, iso-immunization, the chemistry of the serum and serum proteins, the nature and formation of antibodies, the role of histamine in anaphylaxis, the mechanisms producing allergy to sulfonamides, and the blood chemistry of shock.

ALLERGY. *Erich Urbach, M.D.*, with the collaboration of *Philip M. Gottlieb, M.D.* 400 illustrations, 80 tables and charts. 1,100 pp. Grune and Stratton, Inc. Medical Publishers. Price $12.00.

This is a large volume of 1,100 pages, well and interestingly written, and containing many good photographs of skin lesions. The book will doubtless be of great help to all students of allergy. There is quite a bit on the basic principles of allergy and the chemistry of allergens and antibodies. There is much that is helpful on allergic reactions to drugs of various kinds. There are many pages on the principles of treatment.

For the gastroenterologist, chapter twenty-one contains much of interest. Dr. Urbach wisely points out the relation between the cyclic vomiting of children and migraine. Often when one is a little uncertain as to the diagnosis of migraine, it helps greatly to learn that when the patient was a child he or she often came home from school with attacks of so-called bilious vomiting. Those readers who may be disappointed by finding on page 784 so little on the diagnosis of food allergies should turn back to page 221 where there are several pages on dietary studies. Dr. Urbach advises the use of Rowe's elimination diets. He doesn't have much to say about the food-diary method which is useful when attacks come at fairly long intervals. On page 222 he advises the use in some cases of a diet of sugar and water. The reviewer tried this many years ago and had such poor luck with it that he had to quit. Many allergic persons seem to be sensitive to the purely physical irritation induced by a concentrated solution of sugar.

Dr. Urbach says that hyposensitization can be achieved by the administration of slowly increasing quantities of the food allergen but the method takes too long and is not always without danger.

NUTRITION AND PHYSICAL FITNESS. *L. Jean Bogert, Ph.D.* 4th Edit., 500 pages, $3.00. W. B. Saunders.

The entire book is said to have been revised and partly rewritten. There are four new chapters on vitamins and minerals, there is a discussion of the effects on fitness on wartime food conditions, metabolism, and the ductless glands. There are tables showing the composition of many foods.

ABSTRACTS OF CURRENT LITERATURE

FRANKLIN HOLLANDER

Associate Editor in Charge of Abstracts
Mount Sinai Hospital, New York City

STAFF OF ABSTRACTORS

ALBERT CORNELL, New York, N. Y.
MAURICE FELDMAN, Baltimore, Md.
*CHARLES A. FLOOD; New York, N. Y.
M. H. F. FRIEDMAN, Philadelphia, Pa.
IRVING GRAY, Brooklyn, N. Y.
*J. DUFFY HANCOCK, Louisville, Ky.
MANFRED HESS, New York, N. Y.
*THOMAS A. JOHNSON, Philadelphia, Pa.
ALLEN A. JONES, Buffalo, N. Y.
N. W. JONES, Portland, Ore.
*JOSEPH B. KIRSNER, Chicago, Ill.
*HENRY H. LERNER, Boston, Mass.
PHILLIP LEVITSKY, Montreal, Can.
*JESSHIL LOVE. Louisville, Ky.
FRANZ J. LUST, New York, N. Y.
ARTHUR E. MEYER, Flushing, N. Y.
FRANCIS D. MURPHY, Milwaukee, Wis.
H. NECHELES, Chicago, Ill.
FRANK NEUWELT, Gary, Indiana
*SAM OVERSTREET, Louisville, Ky.
DAVID J. SANDWEISS, Detroit, Mich.
MICHAEL W. SHUTKIN, Milwaukee, Wis.
VIRGIL E. SIMPSON, Louisville, Ky.
H. J. SIMS, Denver, Colo.
HENRY TUMEN, Philadelphia, Pa.
*ROBERT TURELL, New York, N. Y.
*EDGAR WAYBURN, San Francisco, Cal.
*JOHN H. WILLARD, Philadelphia, Pa
*C. WILMER WIRTS, Philadelphia, Pa.
*IRVING J. WOLMAN, Philadelphia, Pa.

* In Military Service

[Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25 cents for each complete article, not exceeding 25 pages in length, and 10 cents for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such a manner as found convenient. Address: Microfilm Service, Army Medical Library, Washington, D. C.]

STOMACH

SAHLER, O. D., AND HAMPTON, A. O. Bleeding in hiatus hernia. Am. J. Roent. Rad. Therapy, 49: 433 (Apr.) 1943.

The authors record a series of 221 cases of hiatus hernia in which 32 had either moderately marked anemia or a positive history of gastrointestinal tract bleeding. They further studied a group of 100 consecutive cases to determine the incidence of this form of hernia. Of the 9 cases of hiatus hernia so found (6 females and 3 males), 3 gave a history of vomiting a small amount of blood. Sahler and Hampton believe that there is always some mucosal disturbance in cases of hiatus hernia which bleed. Congestion, gastritis, and ulceration are given as the causes of bleeding. They note that the bleeding is probably due to constriction of the hernial ring with resultant gastritis and ulceration of the herniated fundus. If neither gastritis nor ulceration is present the lesion will not cause bleeding. A detailed analysis of the 32 cases is presented.

MAURICE FELDMAN.

BUSCHKE, F., AND CANTRIL, S. T. Secondary lymphosarcoma of the stomach. Am. J. Roent. Rad. Therapy, 49: 450 (Apr.) 1943.

Buschke and Cantril call attention to a certain type of lymphosarcoma of the stomach secondary to a known focus of lymphosarcoma in some distant part of the body, outside of the abdominal lymphatic area. They point out that the most common site of the primary lesion is the lymphoid tissue of the pharynx, stomach, ileum, and cecum. It is well known that secondary deposits from lymphosarcoma of the pharynx, in their late stages, tend to involve the abdominal lymph nodes. The authors report a case of lymphosarcoma of the pharynx with secondary lymphosarcoma of the stomach. In this case the roentgen examination revealed a large ulceration on the greater curvature of the stomach which resembled a carcinomatous ulcer. Similar cases reported by Schindler and Renshaw are also cited.

MAURICE FELDMAN.

SAHLER, O. D. AND HAMPTON, A. O. Bleeding associated with extramucosal tumors of the stomach. Am. J. Roent. Rad. Therapy, 49: 442 (Apr.) 1943.

"Extramucosal tumors' is used in the broad sense, encompassing different histological varieties. The authors report 24 cases, consisting of 8 leiomyoma, 6 leiomyosarcoma, 4 neurofibrosarcoma, 2 neurofibroma, 2 sarcoma, 2 fibrosarcoma, and 1 fibroma. One case had 2 different types of tumor. Gastrointestinal bleeding is one of the most common symptoms of benign tumors; it occurred in 66.6 per cent of the authors' series. Of the 16 cases with bleeding, there were 9 with ulceration in the tumor, 5 with no ulceration, and 2 in which ulceration is not mentioned. The roentgenological diagnosis of extramucosal intramural tumors of the stomach is dependent on the presence of a smooth or lobulated mass, projecting into the stomach from its wall. The mucosa over the tumor appears smooth and without its normal folds. There is no tendency to spasm or an incisura in these tumors. Two case reports are described in detail.

MAURICE FELDMAN.

HILL, L. C. Dyspepsia in the Army. Lancet, 244: 452 (April) 1943.

The author starts out by saying "It might have been assumed that a greater appreciation of the importance of the problem by the civilian boards would have reduced the intake of potential dyspeptics, but the figures hardly warrant this assumption." He then presents his results of a thorough investigation of 197 dyspeptics at a static military hospital over a period of 7 months. He divides his group into the following: peptic ulcer, duodenitis, functional dyspepsia, and a miscellaneous group which includes achlorhydria, aerophagia, hysterical vomiting, etc. Among the group of functional dyspeptics there are cases which show features analagous to those seen in effort syndrome. He labels this latter group as having "effort dyspepsia." He does not present anything new in the discussion of these groups.

Of interest, however, is his method of disposal of the dyspeptic soldier in this hospital. "All cases of proved ulcer and those diagnosed as duodenitis have been boarded out of the Army and arrangements have been made for their treatment outside. An exception has been made in the case of a few officers and senior NCOs in key positions, who were given a full course of treatment and placed in category C. The psychoneurotics were all referred to the psychiatrist and most of them were boarded out of the Army, either immediately or after institutional treatment. As a group they seemed particularly resistant to treatment of any kind. All cases of chronic gastritis were similarly disposed of, and 2 cases of achlorhydria for the reasons mentioned above. The functional dyspeptics were dealt with on their merits. The decision to board out of the Army, regrade into a lower category, or return to unit without regrading, depend on such factors as the length of history, severity of symptoms, and result of the fractional test-meal. The hypochlorhydric type were particularly resistant to treatment and liable to relapse, and they and the high-acid group were all either regraded and put into a lower category, usually C, or invalided out of the Army. Of the remainder, most were returned to unit after being firmly reassured in a special interview in which every effort was made to remedy any obvious faults or failure to adjust. A few remained slightly disgruntled, but all were made to realise that they had a full investigation and a square deal, and the majority went out prepared to make a fresh start, with every prospect of success."

DAVID J. SANDWEISS.

HELD, I. W. AND BUSCH, I. Cancer of the stomach: With special reference to early diagnosis. Ann. Int. Med., 18: 719 (May) 1943.

Two groups of cases of stomach cancer never reach the operating table: (1) those of a highly malignant nature which spread rapidly to neighboring structures or metastasize to distant ones, and (2) those which remain asymptomatic, being in silent areas. The authors consider cancer from the viewpoint of its origin from either previously healthy or previously diseased mucous membrane. The first is represented by some 70 per cent of all cases. In the remaining 30 per cent, cancer may originate from a site where either

(a) a gastritis, (b) a polyp, or (c) a gastric ulcer is found as a pre-existing lesion. Such patients have had gastric complaints for years and it is difficult to mark a time when a cancer actually began to develop. The diagnosis of gastritis is made a bit easier by use of the gastroscope. Roentgen ray demonstration of incomplete cardiospasm, deformity of the air bag, and imperfect visualization of the cardia may lead to an early diagnosis. Polyps are generally asymptomatic and discovered only accidentally. When single, they may attain a size helpful in diagnosis, and may cause uncontrollable bleeding short of operative intervention. Gastroscopy is often a conclusive diagnostic procedure.

Concerning the development of a cancer or an ulcer base, there is still great difference of opinion; Wilson and McCarty, with their 60 to 70 per cent coincidence, being at one extreme and Schindler, stating that a cancer never develops on an ulcer base, being at the other. Aschoff epitomizes his opinion by stating that "Cancer can frequently ulcerate but an ulcer seldom cancerates." The dictum of Carmen, that a niche on the lesser curvature with a diameter of 2.5 cm. or more should be regarded as malignant, especially if the niche is meniscus-shaped, can no longer be accepted as a safe guide. The authors have seen ulcers 10 cm. in diameter in which the pathologist was unable to demonstrate any malignant cells. Size is not a safe guide but rather the persistence and aggravation of symptoms. It is believed that from 30 to 40 per cent of cancer of the stomach should be found still operable.

VIRGIL E. SIMPSON.

BOWEL

WILLAUER, G. J., AND O'NEILL, J. F. Late postoperative follow-up studies on patients with recurrent appendicitis. Am. J. Med. Sci., 205: 334 (March) 1943.

Histories and follow-up records of 375 cases from the B Surgical service of Jefferson Medical College Hospital, were reviewed. In most instances, these patients were diagnosed preoperatively as subacute or chronic appendicitis; a laboratory record of the removed tissue was available in 255. Of these, 104 cases had appendices which showed no evidence of organic disease, 75 showed lymphoid hyperplasia, 32 cases had a chronic appendicitis, and 21 cases had acute appendicitis. In 48.4 per cent of the patients, symptoms had been present at intervals for 6 months or more, while only 4 per cent gave no history of pain prior to the present illness. Of 15 patients operated upon following their first attack, 14 were symptom free postoperatively. The leucocytes were within normal limits in the majority of the cases. There were 49 cases in which fecaliths were reported in the operative notes; 43 of these had no pain postoperatively. The duration of onset varied from 8 days to 1½ years before operation. In the group with the appendiceal lumen obstructed by fecaliths, 87.8 per cent were symptom-free after operation. Operative scars in 255 cases were painless and well-healed; 2 had weak scars and 4 complained of "bulging." No definite hernias were found. There were 12 cases of keloid formation, and 20 of more or less painful scars. Of the 375 cases of appendicitis, 264 were completely cured of postoperative symptoms following appendectomy and a total of 348 were either completely or partially relieved of pain. The remaining 27 patients had exactly the same post-operative pain as they had had preoperatively. Of these, ⅔ are women with various menstrual and digestive symptoms and possibly a dietary deficiency. Four of the patients were neurasthenics and in such cases appendectomy should not be advised.

ALLEN A. JONES.

DUFF, G. L., FOSTER, H. L., AND BRYAN, W. W. Primary carcinoma of the infra-ampullary portion of the duodenum. Arch. Surg., 46: 494 (Apr.) 1943.

The literature on the clinical, roentgenologic, and pathologic pictures of primary carcinoma of the infra-ampullary portion of the duodenum is reviewed, and an additional case is presented. The clinical symptoms in this patient conformed to the typical clinical picture of epigastric distress with loss of appetite, persistent vomiting, and rapid weight loss. The diagnosis was made roentgenologically. The X-ray revealed the characteristic irregular filling defect of the third portion of the duodenum, with concentric

narrowing of the duodenal lumen and dilatation of the duodenum proximal to the area of narrowing. Pathologically, the tumor was typical of primary carcinoma of the duodenum situated in the infra-ampullary portion of the duodenum on gross examination. When seen under the microscope it appeared to originate from pancreatic tissue. Pancreatic rests in the duodenum and other areas of the body occur more frequently than has been generally believed. Such rests may give rise to tumors, either benign or malignant. It was concluded that in the case presented, the growth was carcinoma arising from such a pancreatic rest in the duodenum.

FRANCIS D. MURPHY.

JACKMAN, R. J., AND SMITH, N. D. Some manifestations of regional ileitis observed sigmoidoscopically. Surg. Gyn. Obs., **76**: 444 (Apr.) 1943.

The anorectal manifestations of regional ileitis were determined in 114 patients all of whom had a sigmoidoscopic examination. In 36 (31.6 per cent) there was an anal abscess or fistula, or a history of operation for anal fistula. In 8 of these 36 persons, the main complaint was anal fistula, and the regional ileitis was revealed later; 17.5 per cent of the patients had an extrarectal mass; 7.8 per cent had anal ulceration or contracture of the anal outlet, 3.5 per cent presented ulceration of the lower part of the bowel after short circuiting operations and resection of the diseased portion. These findings mean that many patients with regional ileitis first come to the physician with a complaint of anal abscess or fistula. The small bowel should be examined for regional ileitis in all young adult patients with any vague intestinal disorder, with anal fistula or with a history of abscess or fistula. Any patient with anal fistula should be given a proctoscopic examination. If an abdominal condition is found, roentgenologic examination of the small intestine and the large intestine is indicated also. Any extrarectal mass of unknown cause, should be studied with regional ileitis in mind.

FRANCIS D. MURPHY.

HENDERSON, J. L. Sulphaguanidine in neonatal epidemic gastro-enteritis. Brit Med. J., 4291: 410 (Apr.) 1943.

The treatment of epidemic gastro-enteritis is discussed. The cause of this condition remains questionable. Attacks have been attributed to various organisms found normally in the bowel, such as B. proteus, B. coli, B. lactis eorogenes, etc. The author has had experience with 6 epidemics, attacking 102 infants. In 3 epidemics, totalling 72 cases in which no specific treatment was used, the mortality ranged from 69 to 86 per cent. In 30 cases which were treated by chemotherapy the mortality was 10 per cent. The treatment outlined involves no initial purge, withholding all milk from the diet, the use of 5 per cent lactose or dextrimaltose in water for feeding, the giving of fluid in an amount of 4 ounces per pound per day, and the use of sulphaguanidine. Milk feeding is resumed only when definite improvement has taken place and a return of appetite is noted, and then it is reintroduced into the diet only gradually. The sulphaguanidine is given to mature infants in a dose of 0.75 g. initially, followed by 0.5 g. every 4 hours. In premature infants a dose of 0.5 g. is given initially and is followed by 0.25 g. every 3 hours. This is continued up to 14 days. All cases are immediately isolated in order to prevent spread of the disease.

HENRY TUMEN.

GOODMAN, M., AND SILVERMAN, I. Acute appendicitis in patients with the common contagious diseases. New Engl. J. Med., 228: 533 (Apr.) 1943.

The records of 29,802 cases of the common contagious diseases were reviewed for the concomitant presence of acute appendicitis; it occurred in 53 cases, an incidence of 0.18 per cent. An analysis of 102 cases of acute appendicitis and pseudoappendicitis was made for age, sex, leukocyte count, and the time relation between the onset of the appendicitis and the manifestation of the contagious disease. More than half the cases of acute appendicitis were found to have already ruptured at the time of operation. It is pointed out that physicians often hesitate to diagnose acute appendicitis in the face of obvious signs because of the presence of a contagious disease. Although it is true that nonappendiceal abdominal symptoms are common during the course of the various communicable diseases, this fact should not

deter one from diagnosing acute appendicitis if there is sufficient evidence. A review of the literature and some of the reported cases are included in this study.

JOSEPH B. KIRSNER.

HELWIG, E. B. Benign tumors of the large intestine—incidence and distribution. Surg. Gyn. Obs., 76: 419 (Apr.) 1943.

A study was made of the occurrence and exact nature of benign tumors of the large intestine. The report is based on studies of 1,460 consecutive autopsies, in which the entire large intestine was available for study. Of the various kinds of polyps, there were 139 adenomas, 13 lipomas, 1 carcinoid, and 1 leiomyoma—in a total of 154 cases. The adenoma is the most common tumor of the large intestine, and occurred most frequently in the sigmoid colon. The second most frequent, the lipoma, is found most commonly in the cecum and ascending colon. Leiomyomas and carcinoids of the large intestine are rare.

FRANCIS D. MURPHY.

LIVER AND GALLBLADDER

GRAY, H. K., AND SHARPE, W. S. Biliary dyskinesia. Arch. Surg., 46: 564 (Apr.) 1943.

This report deals with the problem of persistence of typical preoperative symptoms after cholecystectomy for cholecystic disease. The part played by a remnant of the cystic duct and the effect of its removal were studied in 44 patients. In 31 of these patients, in whom there were adequate indications for cholecystectomy, removal of the stump of the cystic duct and calculi from the common bile duct or from the stump of the cystic duct was done. Symptoms were relieved in 22 of the cases. In 9 cases in whom the indications for cholecystectomy were not adequate, the operation did no good. Biliary dyskinesia may be due to ill-advised removal of the gallbladder with persistence of some functional disorder of the choledochus sphincter, or residual inflammation of the liver, pancreas, or ductile system. It is therefore very important to operate only in cases where there is definite disease of the biliary tract. Care must be taken not to damage the common bile duct during operation, and all but a very small part of the cystic duct should be taken out. When the patient suffers from a persistence of symptoms after operation, and reoperation is thought advisable, a careful search should be made for a remnant of the hepatic duct even though calculi are not suspected in the common bile duct.

FRANCIS D. MURPHY.

ULIN, A. W. Therapeutic trends and operative mortality in cases of obstructive jaundice. Arch. Surg., 46: 504 (Apr.) 1943.

The history of the treatment of jaundiced patients undergoing operation is given. Postoperative hemorrhage, an important cause of operative mortality, has been solved by the introduction of vitamin K, but this vitamin alone does not reduce significantly the fatalities following operative procedures in jaundiced patients. For good results a full therapeutic regimen is necessary. Mistakes which should be guarded against are: (1)Too great reliance should not be placed on tests of prothrombin time and response to vitamin K, with neglect of other liver function tests and clinical impressions. (2) Vitamin K should not be carelessly given but its administration should be adapted to the needs of the individual patient. (3) Supportive therapy, such as blood transfusion, and administration of bile and oxygen, should not be neglected. (4) Preoperative stays should not be too short, and postoperative follow-ups should be done carefully. (5) The diet should not be neglected, but should be adequate and suited to patients with jaundice. Vitamin K should not displace other vitamins. Forty-two operative cases are reviewed with reference to therapy, operative mortality, and postmortem observations. Response to vitamin K as an index of hepatic function is discussed. It is said that prothrombin and tests for prothrombin do not always tell the whole story in obstructive jaundice. The pathologic changes in the liver are described; they included mainly fatty changes, necrosis, infection, sclerosis, degeneration, and malignancy. Some pathology was found in the pancreas, but these are considered insignificant.

FRANCIS D. MURPHY.

EDWARDS, L. R. L. An outbreak of epidemic catarrhal jaundice. Brit. Med. J., 4293: 474 (Apr.) 1943.

The author observed 64 cases of epidemic catarrhal jaundice in 8 months. The majority of these occurred in young school children, the few adults who were attacked being young school teachers. The sex incidence was equal. The cases were seen largely in the spring and summer. The highest age incidence was from 6 to 10 years. The infection seemed to spread by direct contact and droplet infection was suspected. There was no high incidence of sore throat or enteritis. The incubation period seemed to be between 3 and 4 weeks. The clinical picture included malaise, anorexia, vomiting, and upper abdominal pain. The patients were usually constipated, though an occasional bout of diarrhea occurred. Jaundice usually began at the time when the above symptoms stopped, it gradually extended over the body in about 2 or 3 days, and lasted up to about 2 weeks. The stools became acholic. There was variable fever and headaches occurred frequently. The liver was usually large and tender and the spleen was generally palpable. Leukopenia with lymphocytosis and monocytosis occurred. The patients usually complained of generalized aches and pains but pruritus was rare. Edwards is inclined to blame the infection on a filterable virus with respiratory spread. He felt that there was no effective control of the spread of the disease but recommended a 2 week isolation period for those who were attacked.

HENRY TUMEN.

NESBITT, S. Excretion of coproporphyrin in hepatic disease. Arch. Int. Med., 46: 483 (Apr.) 1943.

Porphyrin arises in the body during the synthesis of hemoglobin rather than during its destruction, as had been supposed formerly; a small proportion of isomeric series I arises as a by-product of the main synthesis of isomeric series III, intended for utilization in the manufacture of hemoglobin. The porphyrin of isomeric series I is not utilized and is excreted as coproporphyrin I. Any porphyrin of isomeric series III which has been synthesized in greater amounts than necessary to meet immediate requirements, or which is prevented from entering into the synthesis of hemoglobin by a toxic block (such as occurs with lead poisoning), is excreted as coproporphyrin III. Thus, both coproporphyrins I and III may occur in normal as well as pathological urines. It was supposed formerly that only coproporphyrin I was excreted normally in urine. Coproporphyrin is chiefly excreted by the liver and kidneys, the ratio of urinary to fecal excretion depending chiefly on the potency of the bile passage and efficiency of the liver. A study was made of 10 patients with various types of hepatic damage or biliary obstruction. The urinary coproporphyrin was isolated and the isometric type determined. The occurrence in the urine of coproporphyrin I, either alone or with additional varying proportions of coproporphyrin III, is in accord with the current hypotheses of synthesis and excretion of porphyrin. Coproporphyrin III was excreted alone in but one instance, for which the author has no explanation.

ALBERT CORNELL.

HOOKER, D. H., (CAPTAIN). Exploration of the common bile duct. Am. J. Surg., 60: 88 (Apr.) 1943.

This analysis of 165 cases is concerned with the exploration of the common duct. Women predominated, and the majority of the series were in the 5th and 6th decades of life. The symptom complex was generally characterized by right epigastric pain, nausea, vomiting, eructations, chills, and fever; the latter thermal variations appeared in 64 instances. In 122 cases clinical jaundice was evident. Choluria was present in over half while in approximately $\frac{1}{3}$ the stools were bile negative. Other laboratory findings disclosed leukocytosis in the presence of sepsis, prolonged blood coagulation in a small group and impaired liver function in about $\frac{1}{3}$. X-ray was of value in the preoperative determination of gall bladder function and calculi. Postoperatively, cholangiography is of great value in determining the potency of the common duct. In 22 cases the gall bladder had been removed elsewhere. In this series, 138 received T-tube drainage of the common duct. In the results 120 patients were completely cured, 5 required another operation,

and 22 died. Cardiac failure was the most common cause of death and wound hemorrhage next in frequency; the total mortality was 9 per cent. Exploration of the common duct carries a higher mortality than single cholecystectomy and should be reserved for definite indications.

MICHAEL W. SHUTKIN.

JOHNSIN, F. E., AND BOYDEN, E. A. The effect of sectioning various autonomic nerves upon the rate of emptying of the biliary tract in the cat. Surg. Gyn. Obs., 76: 395 (Apr.) 1943.

The effects of cutting or eliminating certain nervous pathways to the biliary tract of the cat were studied by experimental methods. Cutting the gastroduodenal plexus to the choledochoduodenal junction does not change the rate of emptying of the bile passages after eating, nor does it do away with the inhibitory reflex to the gall bladder from the cecum. This plexus probably is composed of afferent and vasomotor fibers. Emptying is much slower when the gastroduodenal nerve innervating the same junction is cut. This may mean that treatment of spastic sphincter by severing the nerves in the hepatoduodenal ligament of man cannot be of great value. If the right vagus and its celiac division are cut, the flow becomes even slower, which may indicate that the right vagus sends both parasympathetic inhibitory fibers to the sphincter by way of the gastroduodenal nerve, and motor fibers to the gall bladder by way of the hepatic plexus. The fact that severance of the left vagus which does not send fibers to the choledochoduodenal junction retards emptying of the gallbladder, but to a lesser degree, adds weight to this statement.

The emptying time of the gall bladder is by cutting the splanchnic roots of the celiac ganglia as far down as the second lumbar nerve, because the inhibitory reflex from cecum to gall bladder is abolished. Since severance of the gastroduodenal nerve to the sphincter retards rather than accelerates emptying time, this nerve probably does not convey sympathetic fibers which maintain the tone of the sphincter. It is suggested that in fasting the biliary outlet is kept closed by a local mechanism, and that after eating the sphincter relaxes due to impulse from the right vagus and by hormones in the intestinal mucosa. In man, as neuromimetic drugs do not affect the sphincter much, the vagus may have lost this power, and release of the sphincter is accomplished by antispasmodics and hormones only.

FRANCIS D. MURPHY.

ANEMIAS

SACHS, A., LEVINE, V. E., HILL, F. C., AND HUGHES, R. Copper and iron in human blood. Arch. Int. Med., 46: 489 (Apr.) 1943.

There is a reciprocal inverse relation between copper and iron in the blood of human beings. Thus, hypoferronemia is usually followed by hypercupremia, and hyperferronemia by hypocupremia. This relationship is usually constant but occasionally copper fails to respond to a fall in iron. Starvation, high intestinal fistulas, and extremely severe diarrhea are possible factors encouraging a deficiency of copper, but as yet no one has definitely demonstrated a deficiency of this element in a human being. Copper acts as a catalyst with reference to growth, respiration, and hemopoiesis. Iron is absorbed chiefly in the duodenum, to some extent in the jejunum, and to a lesser extent in the ileum. Iron is excreted largely in the bile, feces, and urine. (By means of Thiry fistulas in dogs, the absorption of copper was found to occur in the upper jejunal loop, but not at all in the middle and distal loops.) Copper is excreted mostly in the feces and urine. The authors do not feel that added copper is necessary in the treatment of iron deficiency anemias, especially because copper is present in foods and liquids, and all iron pharmaceutical products contain copper. Hydrochloric acid is of great value in ionizing iron and making it more available. However, the absence of free HCl cannot be supplied by the addition of dilute HCl, but nature accommodates itself to its needs as seen in patients with idiopathic hypochromic anemia who have no free acid. Infections or diarrheas may interfere with iron absorption. Ferrous salts are most easily absorbed. Expensive preparations containing liver extract, vitamins, copper, and iron are of no more value than simple ferrous sulphate.

Occasionally liver extract in adequate doses, given with iron, seems to have some value and should be used.

ALBERT CORNELL.

ULCER

MAHER, M. M., YINNINGER, M. M., SCHIFF, L., AND SHAPIRO, N. Some observations on gastritis and peptic ulcer. Am. J. Med. Sci., 205: 328 (March) 1943.

The authors refer to the work of many investigators who have studied the association of gastritis with peptic ulcer and whose findings establish the frequency and reality of such association. Their own studies are based on observations in 40 patients with peptic ulcer, 28 of whom had satisfactory gastroscopic examinations; 36 had partial gastrectomy and 4 were studied postmortem. The gastroscopic criteria of the various forms of gastritis used in the study were essentially those of Schindler. (The microscopic criteria of atrophic gastritis and its arbitrary gradations were as adopted and given in J. Nat. Cancer Inst., 2: 583, 1942. They consider the presence of hyperplasia as essential to the microscopic diagnosis of hypertrophic gastritis, and Letulle's description of hyperplasia with increase in the width of the gastric mucosa is accepted. The widening due to the infiltration of small round cells, plasma cells and fibrous tissue, as well as that observed when hyperplasia of lymphoid follicles has ensued, is not a true hyperplasia or hypertrophy. When these processes are associated with a decrease in the glandular elements of the mucosa, atrophic gastritis is present. As regards the term "superficial gastritis," the writers do not consider any particular microscopic change as characteristic of the condition.) In 28 cases in which a satisfactory gastroscopy was carried out, the stomach appeared normal in 12 instances. In 10 cases superficial gastritis was present; in 5, hypertrophic gastritis; and in one there was a combination of the two. In no instance were definite atrophic changes found. Further studies by the authors disclosed a discrepancy between the gastroscopic and microscopic diagnoses in these cases. In 12 instances in which the stomach appeared normal at gastroscopy, definite gastritic changes were present in all. In 10 patients in whom a gastroscopic diagnosis of superficial gastritis was made, 4 showed atrophic gastritis and hyperplasia, 3 showed atrophic gastritis, and 3 showed either a normal stomach or an uncertain atrophic gastritis which they considered within normal limits. The writers state that the atrophic gastritis they reported as present microscopically in 28 of 35 cases of gastric cancer was similar to that described in the group of ulcer patients here reported, except for the association of hyperplasia in 10 instances of the ulcer group.

ALLEN A. JONES.

THOMAS, H. M. Peptic ulcer in the Army. Southern Med. J., 36: 287 (Apr.) 1943.

Seventy-five patients with peptic ulcer were admitted to the Station Hospital at Fort George G. Meade during the year from April 29, 1941 to April 19, 1942. Of these, 71 had duodenal lesions; in only 4 patients was the ulcer situated in the stomach. The commonest symptom was persistent moderate abdominal discomfort. There were 5 cases of duodenal ulcer admitted with acute perforation, and 4 with gross hemorrhage. Ninety-three per cent gave a history of symptoms which existed prior to induction. The majority were treated by partial bed rest, an ambulatory ulcer type of diet, aluminum hydroxide and antispasmodics. Only ⅓ of the patients were relieved of their symptoms within the first 2 weeks of treatment. Approximately ⅔ of the entire group continued to have gastric symptoms even after 4 weeks of hospitalization. Repeated roentgenologic study demonstrated evidence of delayed healing in many instances. This response to the treatment employed was considerably slower than has been observed in civilian practice. Eleven soldiers had been in service for years and were members of the regular army; most of them responded well to medical treatment. Forty-seven patients in the group were studied from the neuropsychiatric standpoint; 25 of these presented symptoms of an anxiety state or anxiety neurosis. Most such patients gave the impression that they were really not desirous of making a satisfactory adjustment to army life. Almost all of the patients with obvious anxieties responded poorly to treatment.

Symptoms of anxiety usually persisted throughout the period of hospitalization, or at least until discharge from the Army was definitely assured. Efforts at reassurance were of little or no avail. Those soldiers who were regarded as having relatively stable personalities did comparatively well symptomatically. This study provides further evidence in support of the concept that psychic factors are of paramount importance in the production and continuation of peptic ulcer.

JOSEPH B. KIRSNER.

PINCUS, I. J. Gastro-intestinal disorders as seen in an Army station hospital. Southern Med. J., 36: 284 (Apr.) 1943.

Medical attention in the Army differs considerably from similar care in civilian life. No soldier is returned to his company until it is felt that he is able to do full duty, and requires no medication nor a special diet. Hence, the extent of hospitalization is far in excess of what would be expected in civilian life. Gastrointestinal disorders are extremely common in the armed forces. Functional intestinal complaints and psychoneuroses with gastrointestinal complaints constitute the largest and most difficult group. It is extremely difficult to decide which of the psychoneurotics can be rehabilitated and which ones had best be discharged from the service. This is particularly true since adequate follow up is impossible. The present program of symptomatic treatment and superficial psychotherapy is long drawn out and discouraging. This group of cases is probably best managed by discharge from the Army and return to civilian life. Peptic ulcer is an important and serious problem. Of 21 roentgenologically proved ulcers, 18 were duodenal and 3 were gastric. The large majority occurred in persons who had had ulcers prior to induction. Activation of the ulcer occurred quickly after an ulcer patient was inducted. This development is attributable to emotional disturbances rather than to changes in diet. It seems doubtful that peptic ulcers are more common in the army than in civilian life. Soldiers with proved peptic ulcers are best managed by an honorable discharge from the Army.

JOSEPH B. KIRSNER.

HINTON, J. W. The intractable duodenal ulcer. Ann. Surg., 117: 498 (Apr.) 1943.

The author first emphasizes that the medical management is the treatment of choice in cases of duodenal ulcer and that surgical intervention should be confined to the intractable cases. He then states that in his opinion the only true indication of intractability in a duodenal ulcer is constant pain and that only in cases where no sort of medical management can alleviate the pain should gastric resection be done. In any case of duodenal ulcer, adequate and thorough medical treatment should be tried before rushing into surgery, and that when the operation is indicated, one should perform a subtotal resection and not gastroenterostomy or other procedure. The surgical technique is explained in detail and illustrated, and it is emphasized that the pylorus and the ulcer must be removed in toto.

FRANK NEUWELT.

LORD, J. W. JR., ANDRUS, W. DEW., AND STEFKO, P. Effects of jejunal transplants on experimental production of peptic ulcers. Arch. Surg., 46: 459 (Apr.) 1943.

It had previously been observed that when pedicle grafts of jejunum are transplanted into the stomach wall of dogs, the gastric secretion becomes relatively more alkaline in response to histamine, in contrast to the normal reaction. The report given in this paper confirms this observation in animals given larger doses of the drug for a comparatively long period. It is suggested that such transplants may be useful in preventing the occurrence of duodenal erosions and ulceration during continuous long exposure to histamine. In the one animal in which it was done, implantation of a pedicle graft of jejunum into the stomach wall resulted in healing of duodenal lesions although injections of histamine were continued. The results of these experiments may have an application clinically. Pedicle grafts of jejunum transplanted to the gastric wall remain viable for a long time when their blood supply is intact. Further experimental work is being done in order to discover the value of such transplants and their mode of action.

FRANCIS D. MURPHY.

PROCTOLOGY

CATTELL, R. B. AND WILLIAMS, A. C. Epidermoid carcinoma of the anus and the rectum. Arch. Surg., 46: 336 (March) 1943.

Epidermoid, or squamous cell carcinoma, of the anus has been looked upon as a highly malignant condition in which the outcome is almost always unfavorable in spite of treatment. The poor results, however, may be due to inadequate treatment. The subject is not given enough attention in textbooks, and investigations on the matter have not been sufficiently thorough. This paper summarizes the pathologic and clinical aspects of this disease. Ten cases of squamous cell carcinoma were reviewed; 9 were anal tumors and one was in the rectosigmoid.

The incidence of epidermoid carcinoma of the anus is less than 5 per cent of all rectal and anal tumors, and women are affected more than men. It is commonest in those between 50 and 60 years of age, but the age incidence is variable. Antecedent lesions are important etiologically, especiallychronic fistulas and scars due to fistulectomy. All rectal and anal lesions, even though they appear benign, should be examined with cancer in mind, and when any suspicion is present, a biopsy should be done. All tissue removed during operation for supposedly benign conditions should be examined microscopically for cancer. There are no diagnostic symptoms. The gross appearance may simulate fistula, fissure, chancre, condyloma, hemorrhoid, or other rectal diseases. Definite diagnosis may be done only with the microscope. Epidermoid cancer of the anus is similar to epidermoid carcinoma of the skin elsewhere. The condition may metastasize to the sphincter ani muscles, the perianal tissue and rectovaginal septum, the prostate, rectal wall, and rectum. Metastasis may occur by way of the lymphatics or blood vessels. Radical operation gives the best prognosis, and a Miles abdominoperineal resection and radical inguinal dissection is best. For recurrences or inoperable conditions, irradiation is indicated.

FRANCIS P. MURPHY.

PHYSIOLOGY: MOTILITY

LEWIS, J. H., AND SARBIN, T. R. Studies in psychosomatics. I. The influence of hypnotic stimulation on gastric hunger contractions. Psychosomatic Med., 5: 125 (Apr.) 1943.

These experiments were designed to test the extent and nature of somatic response to psychological stimulation. Hunger contractions have been studied extensively since the original work by Carlson and his collaborators. We know now that the functional activity of the stomach may be influenced by a host of external factors. The precise effects of such factors (physical, chemical, pharmacological, etc.) have been studied extensively, but the effects of psychological factors on hunger contractions have hardly been observed. In this study the latter were studied in normal and hypnotized individuals by means of the usual balloon technique. Each subject was queried as to food preferences and a fictitious meal of these choice dishes was "fed" to each individual at the height of the contractions, approximately in the middle of the period of hunger contractions. Eight subjects were used and the psychological "meal" was given both in the normal and hypnotized states. As a check upon this the subjects were given arithmetic problems to solve at other times to see whether the inhibitions caused by the fictitious feedings were the result of distraction of attention rather than the intrinsic meaning of the stimulus-event to the subject. Results showed that in the deeply hypnotized subject the psychological meal generally caused complete inhibition of gastric hunger contractions and the feeling of satisfaction ordinarily evoked by a satisfying meal. The solving of arithmetic problems caused only a transient inhibition. No effects were obtained by means of such fictitious feedings in the normal non-hypnotized subject.

FRANK NEUWELT.

PHYSIOLOGY: ABSORPTION

VERMEULEN, C., OWENS, F. M. JR., AND DRAGSTEDT, L. R. The effect of pancreatectomy on fat absorption from the intestines. Am. J. Physiol., 138: 792 (April) 1943.

Temporary hyperlipemia, which may be produced in normal dogs by the oral administration of neutral fat or fatty acid, is abolished by removal of the pancreas and is not restored by the administration of active pancreatic juice or raw pancreas. Pancreatectomy produces a varying degree of impairment in the absorption of neutral fat, but some animals may still absorb 75 per cent or more of the fat in the diet. Pancreatectomy produces a definite impairment in the absorption of fatty acid, though not so great as in the case of neutral fat.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

WILLIAMS, R. D., MASON, H. L., CUSICK, P. L., AND WILDER, R. M. Observations on induced riboflavin deficiency and the riboflavin requirement of man. J. Nutrit., 25: 361 (Apr.) 1943.

Four subjects were maintained for 288 days on a standard diet containing only 0.35 mg. of riboflavin per 1000 cals., but adequate in other factors of the vitamin B complex. The only evidence of deficiency observed was progressive decrease of excretion of a test dose of 2.0 mg. of sodium riboflavin. Two subjects were maintained on the same standard diet for a period of 246 days but did not receive supplements of crystalline vitamins. This moderately severe restriction of the B complex did not produce the clinical syndrome of riboflavin deficiency. Two subjects maintained on the same standard diet for a period of 288 days were given crystalline riboflavin in addition to other vitamins of the B complex. Evidence of deficiency of any kind was not observed. An intake of 0.8 mg. of riboflavin per 1000 cals. was not associated with depletion of tissue stores of riboflavin, whereas an intake of 0.35 mg. per 1000 cals. definitely was so associated. An intake of 0.5 mg. per 1000 cals. appeared to be close to the daily requirement necessary for maintenance of satisfactory tissue stores of riboflavin. This value therefore appears to approximate closely the minimal daily requirement for riboflavin.

ARTHUR E. MEYER.

BOEHRER, J. F., STANFORD, C. E., AND RYAN, E. Experimental riboflavin deficiency in man. Am. J. Med. Sci., 205: 544 (Apr.) 1943.

The authors call attention to the demonstration by other workers that superficial keratitis results from riboflavin deficiency and they studied the time relationship in its development. From the Students' Health Service of the University of Minnesota diet table, for the benefit of those students requiring dietary management for any cause, a group of 6 volunteers (1 male and 5 females) were chosen. Three of these constituted an experimental group and three made up a control group, the members of which received without their knowledge a daily supplement of 3 mg. of riboflavin. The experimental group received 471 μg. of riboflavin daily. All 6 received vitamin and mineral supplements. The 6 students reported for slitlamp testing at the beginning of the period and twice a week thereafter. In the experimental group on a diet of 1300 calories and 471 μg., 2 subjects developed aphthous stomatitis but no objective evidence of glossitis. In all 3, by slitlamp findings, no abnormalities were demonstrated. Of the control group, one showed a few streamers of the nasal limbus of the left eye on the 22nd day, and fine capillary streamers were found also in the other eye on the 29th day—thus demonstrating minimal, but definite abnormality.

ALLEN A. JONES.

CLAYTON, M. M. AND BORDEN, R. A. The availability for human nutrition of the vitamin C in raw cabbage and home-canned tomato juice. J. Nutrit., 25: 349 (Apr.) 1943.

The availability of the vitamin C in raw cabbage and home-canned tomato juice was studied on 4 young, healthy subjects. The utilization of the vitamin C of each test food was compared with that of pure vitamin C tablets. The basal diet used was neutral in reaction and the subjects were saturated before each test period. Judging from the results of both blood and urine analyses, the vitamin C of both raw cabbage and tomato juice was utilized as well as, or possibly better than, that in the tablets. An

average of 116 g. of the cabbage or 208 ml. (⅞ cup) of the tomato juice used in this experiment provided 50 mg. of vitamin C.

ARTHUR E. MEYER.

RUSSELL, W. O. AND CALLAWAY, C. P. Pathologic changes in the liver and kidneys of guinea pigs deficient in vitamin C. Arch. Path., 35: 546 (Apr.) 1943.

A group of guinea pigs was placed upon a vitamin C deficiency diet and 1 per cent trypan blue in physiologic solution of sodium chloride was injected subcutaneously into the flanks on alternate days—until a total of 200 mg. of the dye had been given to animals weighing from 400 to 600 gm., and 80 mgm. to young animals weighing 150 to 200 gm. The same amount of the dye was given to a control group the animals of which were fed on the same diet plus daily intraperitoneal injections of ascorbic acid. Blocks of liver, spleen, kidney, adrenal gland, intestine, lung, and heart muscle were fixed in 3 per cent solution of formaldehyde, and paraffin sections stained lightly with trinitrophenol (picric acid). The granules of the dye were plainly visible.

Sections of the liver and kidney from the scorbutic animals showed remarkably more trypan blue than the sections from the corresponding control animals. There was no significant difference in the amount of the dye in the other organs examined. The livers of the scorbutic guinea pigs showed moderate to advanced fatty degeneration of the parenchymal cells, particularly in the region of the central veins. These cells showed the greatest deposition of the dye granules. The cells of the convoluted tubules of the kidney showed heavy masses of the dye deposited in them. In the same cells from the kidneys of the control animals there was a deposition of the dye, but to a much less extent. Histologically there was observed no change in the kidney cells of scorbutic animals to account for this difference in storage, but the latter was interpreted as indicating a probable pathologic change in these cells. The changes in the liver were regarded as evidence of hepatic damage from vitamin C deficiency.

Other investigators have advanced evidence that vitamin C is concerned with the metabolism of the aromatic amino acids. Disturbed metabolism was eradicated completely by the administration of ascorbic acid, whereas other vitamins were ineffectual. Since the liver is believed to play an important part in the metabolism of amino acids, the pathologic change in the liver cells, as described, was considered morphologic evidence in support of this idea also.

N. W. JONES.

PHARMACOLOGY

PAUL, W. D. The effect of acetylsalicylic acid (aspirin) on the gastric mucosa. J. Iowa State Med. Soc., 33: 155 (April) 1943.

Douthwaite and Lintott had seen gastroscopically irritation, hemorrhages and inflammation of the stomach following the intake of aspirin. Paul has checked these studies by a great number of his own gastroscopic observations and obtained opposite results. In 107 patients with a normal mucosa, acetylsalicylic acid caused no hyperemia, edema, or hemorrhage. In 62 cases of gastritis it was difficult to decide whether pigment spots, submucosal hemorrhages, or color changes were the result of the action of the drug. Peristaltic waves were observed which removed the drug to another part of the gastric mucosa, and in this new place no new hemorrhages developed. Several patients, reexamined without being given any drug, presented the same changes observed before. Many controls in patients with peptic ulcer and in psychoneurotic individuals with normal mucosa led to the conclusion that acetylsalicylic acid in doses as high as 80 grains per day does not cause any gastroscopically demonstrable changes in the stomach.

RUDOLF SCHINDLER.

MISCELLANEOUS

BONNE, C. Invasion of the wall of the Human intestine by ancylostomes. Am. J. Trop. Med., 22: 507 (Sept.) 1942.

The author reports 5 additional cases of invasion of the intestinal wall by Ankylostoma duodenali. Necator americanus, the most common hookworm in Java, does not display this invasive properly, apparently

because of its lack of teeth. The invasion usually takes place in the jejunum, although the ileum or even the colon are not immune. An extensive hemorrhage and inflammatory reaction accompany the penetration, but do not endanger the life of the host.

PHILLIP LEVITSKY.

FEINBERG, S. M., ALT, H. L., AND YOUNG, R. H. Allergy to injectable liver extracts: Clinical and immunological observations. Ann. Int. Med., 18: 311 (March) 1943.

The authors introduce 8 case reports with a brief bibliography calling attention to the importance and significance of reactions from injectable liver extracts. They found only 29 cases in the literature exclusive of their 8. They conclude from their experience that reactions are more common than the literature would indicate, and that some of them are of the nature of an atopy, while other reactions followed injections that had previously been tolerated. It is suggested that the long interval method of injections allows more ready sensitization, and data are offered to support the opinion that there may be a special type of antigen which causes easy sensitization. Solutions of the problem offered are: temporary discontinuance of injections, selection of an extract derived from another species of animal, in more difficult cases the usual plan of desensitization, and the oral use of liver. Attention is arrested by this report, chiefly through the suggestion of the potential immunologic significance of either an antigen in a fraction of organ tissue or of one containing no protein yet capable of causing skin reactions.

VIRGIL E. SIMPSON.

ROSE, J. A. Eating inhibitions in children in relation to anorexia nervosa. Psychosomatic Med., 5: 117 (Apr.) 1943.

This article approaches the subject of anorexia nervosa in an interesting manner from the psychiatric or psychosomatic aspects of the condition. In some ways the author's approach is a dialectical one, but at times he becomes a bit vague, due perhaps to technical verbiage. The point is brought out that clinicians have devoted much attention to the somatic aspects of anorexia nervosa while neglecting a formulation of its etiological dynamics. The author states that from the standpoint of positive diagnosis, early treatment, and prevention, understanding of the way in which the condition develops is of greater importance than a knowledge of the morbid physiology of the advanced condition. A series of cases are presented to illustrate various aspects of the problem, how children may be poor eaters due to disturbances in the normal behavior pattern; while the majority of feeding problems may be due to overconcern of the parents, yet many have a definite psychiatric background. At times it is hard to accept the profoundity of the problem in children so young. Such psychiatric difficulties are accepted more easily in postpubertal children or young adults. Emphasis as to therapeutics is placed on change in the present; i.e., allow the patient to overcome his present resistance and not attempt to make up to the patient what the parent was unable to give.

FRANK NEUWELT.

SHAFIROFF, B. G. P., DOUBILET, H., SIFFERT, R., AND COTUI, F. The effect of hemorrhage on normal and hypocoagulable blood and lymph. Am. J. Physiol., 138: 753 (April) 1943.

Rapid progressive hemorrhage rendered the blood and lymph of normal animals hypercoagulable. Rapid progressive hemorrhage also caused a marked reduction of the clotting time in animals whose blood was experimentally rendered hypocoagulable. The mechanism for increased coagulability of the blood during hemorrhage was related to the increased mobilization of thromboplastin. The lymph of protamine and peptone injected animals remained hypocoagulable in spite of hemorrhage.

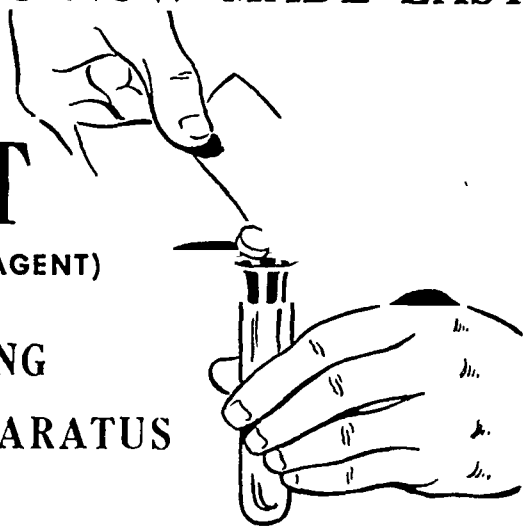
ARTHUR E. MEYER.

URINE-SUGAR TESTING NOW MADE EASY

WITH

CLINITEST

(COPPER REDUCTION TABLET REAGENT)



NO FLAME NO HEATING

NO COMPLICATED APPARATUS

NO WATER BATH

JUST DO THIS:

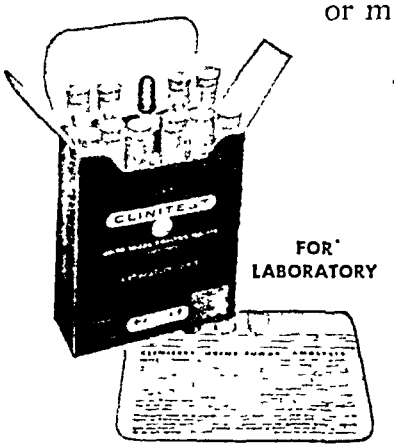
Add 1 Clinitest Tablet to proper amount of diluted urine in test tube provided. . . . Allow for reaction. . . . Compare with color scale.

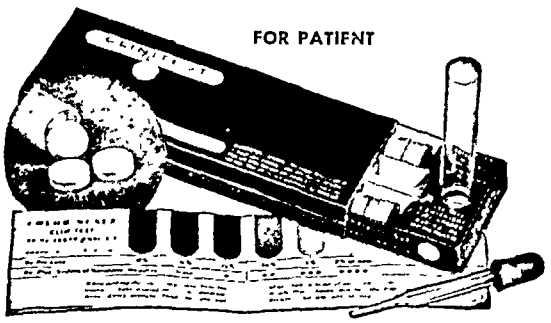
Simple . . . ISN'T IT?

No powder to spill—no measuring. . . . Test takes a matter of seconds!

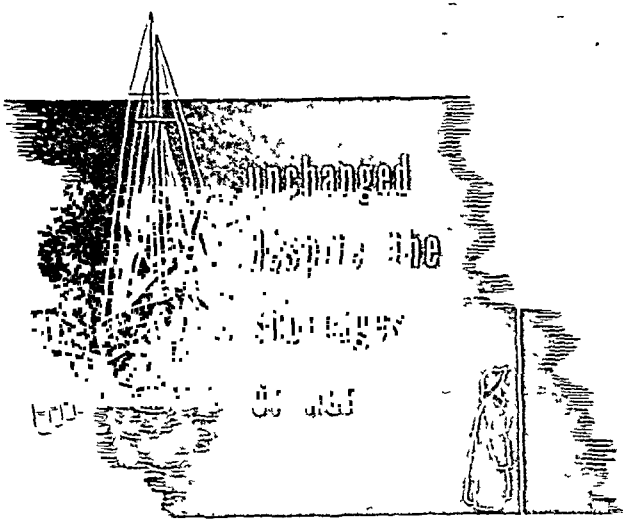
Available through your prescription pharmacy or medical supply house.

Write for full descriptive literature. Dept. G. 1.





EFFERVESCENT PRODUCTS, INC.
ELKHART, INDIANA



you can still prescribe—and your patients can still obtain—the natural vitamins of time-honored cod liver oil itself, in the three pleasant dosage forms of

white's cod liver oil concentrate

. . . drop dosage for infants; tablets for youngsters and adults; capsules for somewhat larger dosage, or wherever capsular medication is preferred.

No Increase in Cost-to-Patient

Despite its advantages in potency, stability, palatability and convenience, the cost of White's Cod Liver Oil Concentrate has always compared favorably with that of plain cod liver oil. Current shortages, however, have resulted in much higher prices for the plain oil, while the price to patient of White's Cod Liver Oil Concentrate has been maintained at its established economy level. Prophylactic antirachitic dosage for infants STILL costs less than a penny a day. Council accepted; ethically promoted. White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

ACCEPTED AMERICAL MEDICAL ASSN

White's

IN HYPOPROTEINEMIA WITH DEHYDRATION

WHEN PLASMA AND DEXTROSE IN SALINE ARE INDICATED

for Safety's Sake, choose

BAXTER EQUIPMENT

A uniform technique which is easy to teach, easy to learn, easy to perform . . . a minimum of accessories and containers for blood collecting, plasma preparation, pooling, banking, and dispensing . . . unbroken asepsis through every step —make the Baxter program simple, economical, and safe.

PRODUCTS OF
BAXTER LABORATORIES
Glenview, Illinois • College Point, New York • Acton, Ontario • London, England
PRODUCED AND DISTRIBUTED IN THE ELEVEN WESTERN STATES BY DON BAXTER, INC., GLENDALE, CALIFORNIA

Distributed east of the Rockies by
AMERICAN HOSPITAL SUPPLY CORPORATION
CHICAGO • NEW YORK

MAKE **KONDREMUL** THE "ACTIVE FACTOR"

IN "MORBID INACTIVITY OF THE BOWEL" (CONSTIPATION)

Mixing thoroughly with the fecal mass, Kondremul stimulates peristaltic action and encourages natural elimination

Kondremul is made with Irish Moss (Chondrus crispus) and contains 55% of mineral oil By a special emulsifying process, the oil is split up into uniformly fine particles and the use of Chondrus crispus minimizes the tendency to break down and release of free mineral oil

In short, Kondremul maintains an even dispersion all the way through the gastro intestinal tract

Indicated in three types of constipation resistant cases, atonic constipation and simple constipation

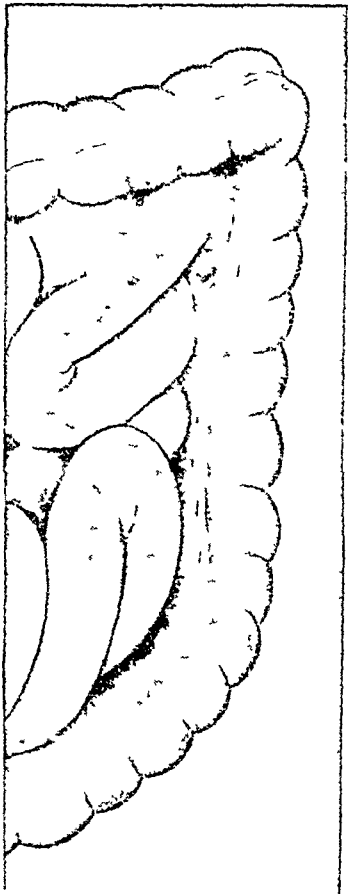
Supplied in three forms to suit each patient type

KONDREMUL PLAIN—for simple constipation Permits smooth, voluntary elimination

KONDREMUL WITH NON-BITTER EXTRACT OF CASCARA*—for atonic, senile and pregnancy constipation

KONDREMUL WITH PHENOLPHTHALEIN* (2 2 grains phenolphthalein per tablespoonful)—for obstinate cases

*CAUTION Should not be used when abdominal pain, nausea, vomiting or other symptoms of appendicitis are present



THE E. L. PATCH COMPANY • Boston, Mass.

Send for your copy of booklet—
"Bowel Hygiene in Rectal Diseases"

(In writing to advertisers, please mention the journal—it helps.)

No Confusion...

..Only *one type* ZymenoL

Equally Effective in CONSTIPATION-COLITIS-DIARRHEA

Different types or combinations are not needed because ZymenoL is a *Natural Approach* to the two basic problems of Gastro-Intestinal Dysfunction:

NORMAL INTESTINAL CONTENT ASSURED
..Through Brewers Yeast Enzymatic Action.*

NORMAL INTESTINAL MOTILITY RESTORED
..With Complete Natural Vitamin B Complex *

This two-fold natural therapy restores normal bowel function without catharsis, artificial bulkage or mineral oil leakage.

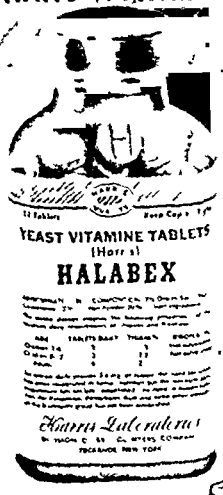
Teaspoon Dosage Economical Sugar Free

Write for Free Clinical Size

*ZymenoL Contains Pure Aqueous Brewers Yeast (no live cells)

OTIS E. GLIDDEN & COMPANY, INC. EVANSTON, ILLINOIS

HARRIS VITAMINS ARE NEVER PROMOTED TO THE PUBLIC



Physical Fitness and Fatigue

DEMAND THE COMPLETE B-COMPLEX FROM NATURAL SOURCE

HARD physical work, even for a few days, requires adequate intake of the vitamin B-complex if physical fitness is to be maintained. This conclusion was made in a well-controlled study* showing the need for natural source vitamin products. The use of thiamin alone on human subjects did not succeed, but the natural source material, a complete and adequate supplement, did give desired results. When the vitamin B-complex was indicated, the natural product such as yeast was considered a sure source of all the necessary components.

*Johnson, R. E., et al — Journal of Nutrition, Dec. 1942

YEAST VITAMINE TABLETS (Harris) • new name HALABEX • have been used by physicians with outstanding success since 1919. They contain (YEAST CONCENTRATE) all factors of the water-soluble B-complex as found in brewers' yeast, the source material. No synthetics are added. High concentration makes massive oral doses easy.

HARRIS VITAMIN PREPARATIONS NOW EMBRACE:

Halabex • Halapan • Haladee
Lamilets • Nicotinic Acid • Vitamin C
Vitamin B_1 • Vitamin B_2

HARRIS QUALITY

Harris Laboratories
(Division of Bristol-Myers Company)
Tuckahoe, N. Y.

PRODUCERS OF VITAMINS FOR MEDICAL USE SINCE 1919

HARRIS LABORATORIES Dept G
Tuckahoe, N. Y.

I would like a trial package of Yeast Vitamine Tablets and information on new HARRIS Vitamin Preparations.

Name_____

Address_____

City_____ State_____

(In writing to advertisers, please mention the journal—it helps.)

GASTROENTEROLOGY

Owned by and Official Publication of the
American Gastroenterological Association, Inc.

Issued monthly, two volumes a year. Subscription price $3.00 per volume. For countries outside the Postal Union, add 25 cents a volume. Subscriptions of members of the Association are included in membership dues and are handled by the Association. Send other subscriptions to the publishers or agents listed below.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of that volume be out of print when subscription is received, the pro-rata value will be credited to the next volume, and renewal invoice adjusted accordingly.

Subscriptions should be renewed promptly. The publishers cannot guarantee to supply back issues on belated renewals.

Claims for copies lost in the mails must be received within 30 days (domestic). Changes of address must be received within two weeks of the date of issue. For the duration of the war, delivery overseas is at the subscriber's risk.

Correspondence concerning business matters should be addressed to the publishers.

INSTRUCTIONS TO AUTHORS

GASTROENTEROLOGY invites clinical and investigative contributions of interest to general practitioners as well as to specialists, which deal with the diseases of digestion and nutrition, including physiological, biochemical, pathological, parasitological, radiological and surgical aspects. Reviews, editorials, abstracts, and book reviews will be provided by the Editorial Board.

Submission of a paper implies that it will not be published elsewhere. Papers will be published within 3 or 4 months after receipt, in order of their receipt, except when revision is required.

Address manuscripts and correspondence pertaining thereto to:

DR. W. C. ALVAREZ, *Editor*
Mayo Clinic
Rochester, Minnesota

DR. A. C. IVY, *Assistant Editor*
303 E. Chicago Ave.
Chicago, Ill.

Manuscripts should be carefully prepared according to the following instructions:

Type written copy, double spaced with a 1 5 inch margin on the left Tables, references, footnotes and figure-legends on separate sheets Construct illustrations and tables with the page size of the journal in mind, arranged to conserve vertical space Glossy prints of photographs are preferable Graphs on white board or blue-lined heavy paper, with lettering and guidelines in India ink. Illustrations that require retouching or redrawing not accepted unless expense is defrayed by the author. A reasonable amount of tables and illustrations is allowed without charge, important additional material may be allowed at cost to the author, at the discretion of the editor.

Number references serially in the text and list them at the end of the paper in the same order. They shoud conform to the Quarterly Cumulative Index Medicus Author's name and initials, journal, volume (arabic), initial pages, and year. Omit title of article

Journal is not responsible for loss of manuscript in the mail. Authors should retain a copy.

Galley proofs are sent to the author. Alterations in type or illustrations will be charged to the author if they exceed 10% of the cost of original composition.

Reprints will be furnished when ordered in advance Their number will be limited only when such sale is prejudicial to the interest of the Journal A table showing cost of reprints, with an order slip, is sent with proof.

AGENTS

For Australia: Angus & Robertson, Limited, 89-95 Castlereagh Street, Sydney.

For the British Empire, except Australia and Canada: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, WC. 2, London, England.

For Canada: Wm. Dawson & Sons, Ltd., 70 King Street East, Toronto.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals

Mt. Royal and Guilford Aves., Baltimore-2, Md., U. S. A.

PUBLISHERS OF *Medicine, Journal of Urology, Journal of Pharmacology and Experimental Therapeutics, American Journal of Tropical Medicine, Journal of Immunology, Journal of Industrial Hygiene and Toxicology, Quarterly Review of Biology, Journal of Bacteriology, Chemical Reviews, Soil Science, Social Forces, Journal of Comparative Psychology, Journal of Organic Chemistry, Occupational Therapy and Rehabilitation, The American Journal of Clinical Pathology, Journal of Physical Chemistry, Philosophy of Science Medical Classics, Journal of Investigative Dermatology, Bacteriological Reviews, Human Fertility, Medical Care, Psychosomatic Medicine, Gastroenterology*

BLAND FOOD QUALITY
IN THE ULCER REGIMEN

In a consideration of the diet needs of the chronic ulcer patient, Cecil* stresses the need for eliminating "all food which can irritate the stomach mechanically."

The bland character of Horlick's, its negligible curd tension and unusual ease and rapidity of digestion render it ideal in the dietetic management of these difficult cases.

Moreover, Horlick's is pleasant to take—on the one hand it avoids the rather flat taste of milk and on the other it is not cloying to the palate.

Note that the convenient pocket flask of Horlick's Tablets may be carried on the person or kept in the office desk drawer for between-meals' feedings.

*CECIL, R. L.:
A Textbook of Medicine,
5th Edition, W. B. Saunders Co.

Recommend

HORLICK'S

The *Complete* Malted Milk—Not Just a Malt Flavoring for Milk

(In writing to advertisers, please mention the journal—it helps.)

PROOF FROM THE LABORATORY

There IS a Difference in Vitamin B Sources

THE BETA-CONCEMIN FORMULA is based on a special fraction of liver that is rich in the whole vitamin B complex as it is found in this complete, natural source. It is adjusted by addition of crystalline B vitamins to assure adequate intake of those B complex factors known to be important in human nutrition and found deficient most frequently in clinical practice.

Pharmacological studies reveal that the Special Liver Fraction used in Beta-Concemin, *when administered in addition to all the established vitamins*, supplies other factors essential for life, growth, hemoglobin formation and normal cutaneous structure. It contains the recently identified anti-anemic component, vitamin B_c.

BETA-CONCEMIN

Brand of B Vitamins

Potent, Complete Vitamin B Complex

Pleasant, fruit-flavored Elixir Beta-Concemin is supplied in 4-oz. and 12-oz. bottles; dosage is 2 or 3 teaspoonfuls daily. Convenient Beta-Concemin Tablets are in bottles of 100; 4 to 6 tablets are given daily.

•

Capsules Beta-Concemin with Ferrous Sulfate are expressly designed for treating iron deficiency anemias. Dosage is 4 to 6 daily. Bottles of 100.

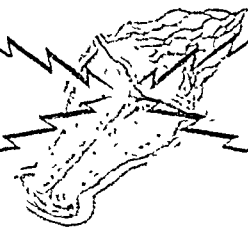
T. M. "Beta-Concemin" Reg. U. S. Pat. Off.

MERRELL
116th Year

THE WM. S. MERRELL COMPANY · CINCINNATI, U. S. A.

Attacks Spasm from 2 angles:

1 MUSCULOTROPIC
—local action upon muscle



NEUROTROPIC 2
—through nerve supply to smooth muscle

—thus providing relief whether spasm is of muscular or neural origin

PAVATRINE

This potent, safe, non-narcotic antispasmodic is a recent result of intensive research in the Searle laboratories.

In dysmenorrhea, gastrointestinal and urinary bladder spasm—PAVATRINE has shown high spasmolytic potency, ability to abolish uterine contractions, increased safety.

While Pavatrine is non-narcotic, its action in dysmenorrhea has been described as *morphine-like.*

Literature showing the smooth muscle relaxing action of Pavatrine, together with dosage and administration, is available. Please address your request to the Searle Medical Dept., P.O. Box 5110—B, Chicago 80, Illinois.

Pavatrine is supplied in bottles of 20, 100 and 1000 s.c. tablets of 2 grs. each.

G·D·SEARLE & CO.
ETHICAL PHARMACEUTICALS SINCE 1888
CHICAGO
New York Kansas City San Francisco

Pavatrine is the registered trademark of G. D. Searle & Co.

SEARLE
RESEARCH IN THE SERVICE OF MEDICINE

(In writing to advertisers, please mention the journal—it helps.)

HILARIOUS
PROTOZOOLOGY

Robert Hegner *knows how to tell a scientific story humorously.*

Big Fleas
Have Little Fleas

or Who's Who among the Protozoa

is a large volume of 290 pages with over 100 scientific drawings and microphotographs and 80 cartoons. **$3.00**

You will enjoy it:

"Sense of humor like that of the renowned James Thurber."—*Journal of A M.A*

"Lewis Carroll would have gnashed his teeth to think he had not written it."—*American Journal of Clinical Pathology*

The Williams & Wilkins Company

BALTIMORE, MARYLAND

ULCER THERAPY

Rx Milk and Cream 90cc.
Tri-Calsate 2 to 4 grams
Stir and drink slowly

The combination supplies both neutralizer and nutriment, eliminating about half the daily routine Tri-Calsate does not make the stomach contents alkaline and its citrate content acts to break down the large curds, making the milk more easily digested and affording greater combining surface to the gastric HCl

Write for trial package and literature

F. H. PAXTON & SONS, INC.
469 E. OHIO ST. *Manufacturing Pharmaceuticals* CHICAGO, ILL

Pepsencia
WITH VITAMIN B_1

PEPSENCIA with VITAMIN B_1 contains the gastric enzymes, pepsin and rennin, coagulable nucleo-proteins, and all of the soluble constituents of the gastric juice. Made directly from fresh hog stomach linings and calf rennets. VITAMIN B_1 has been added in the proportions of 125 U.S.P. units to each teaspoonful.

PEPSENCIA with VITAMIN B_1 is rigidly standardized, is stable, and is pleasant to take.

The recommended daily dosage supplies 375 U.S.P. units of vitamin B_1—equivalent to 12% more than the normal daily requirement as established by the Food and Drug Administration.

Originated and made by

FAIRCHILD BROS. & FOSTER

NEW YORK 13, N. Y.

THE SUNSET YEARS AND *Adequate Nutrition*

As the degenerative processes gain the upper hand during the last decade or two of life, profound changes occur in many metabolic mechanisms. The gastrointestinal tract for example becomes less tolerant of abuses, and difficulty is experienced in digesting some foods which formerly did not prove troublesome. The loss of vigor characteristic of senescence can easily be aggravated to a point of incapacitation if eating habits are not altered to prevent nutritional deficiencies. For only by properly satisfying the nutritional requirements can strength be maintained.

Ovaltine is well tolerated by elderly persons. It supplies a wealth of nutrients which are frequently lacking in the diets chosen during advanced years: biologically adequate protein, B complex vitamins, essential minerals, and vitamins A and D. The high content of diastatic malt makes Ovaltine a valuable aid in the digestion of starchy foods. This delicious food drink appeals to older persons; hence it can be included in their diet three times daily without meeting with objection or resistance. The Wander Company, 360 North Michigan Avenue, Chicago, Illinois.

Ovaltine

Three daily servings (1½ oz.) of New Improved Ovaltine provide:

	Dry Ovaltine	Ovaltine with milk*		Dry Ovaltine	Ovaltine with milk*
PROTEIN	6.0 Gm.	31.2 Gm.	VITAMIN A	1500 I.U.	2953 I.U.
CARBOHYDRATE	30.0 Gm.	62.43 Gm.	VITAMIN D	405 I.U.	480 I.U.
FAT	2.8 Gm.	29.34 Gm.	THIAMINE	.9 mg.	1.296 mg.
CALCIUM	.25 Gm.	1.104 Gm.	RIBOFLAVIN	.25 mg.	1.278 mg.
PHOSPHORUS	.25 Gm.	.903 Gm.	NIACIN	5.0 mg.	6.9 mg.
IRON	10.5 mg.	11.94 mg.	COPPER	.5 mg.	.5 mg.

*Each serving made with 8 oz. milk; based on average reported values for milk.

(In writing to advertisers, please mention the journal—it helps.)

INDEX TO ADVERTISERS

VALENTINE'S MEAT EXTRACT

1871 1944

Has long been used by the Medical Profession both here and abroad for various types of gastric distress.

PALATABLE

READILY ASSIMILATED

READILY ADMINISTERED

VALENTINE'S
MEAT JUICE COMPANY
RICHMOND, 9, VIRGINIA

KONSYL

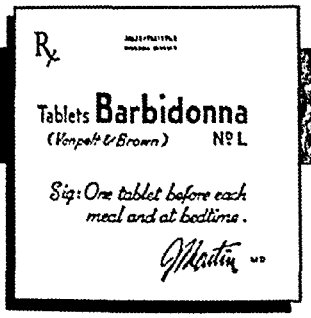
Restores Normal Bowel Function
by
WATER RETENTION AND LUBRICATION

A constructive means of restoring normal intestinal peristalsis through a safe, non-irritant preparation of concentrated vegetable mucilloid made from Plantago Ovata.

Particularly recommended for catarrhal colitis and functional disturbances caused by colonic stasis.

Write for clinical test samples and literature.

BURTON, PARSONS & CO.
WASHINGTON, D. C.



BARBIDONNA

TABLETS

The Modern

ANTISPASMODIC and SEDATIVE

BARBIDONNA TABLETS are specially compounded to meet the exacting requirements of the medical profession. They are time tested and acclaimed eminently effective.

FORMULA
Each Tablet Contains PHENOBARBITAL—¼ gr. BELLADONNA ALKALOIDS (hyoscyamine, atropine and scopolamine) equivalent approximately to 5 minims of Tr. Belladonna.

Supplied in Bottles of 100 and 500 Tablets

BARBIDONNA is a balanced blend of the principal belladonna alkaloids—*hyoscyamine, atropine and scopolamine—with phenobarbital.* Its properties exert central and peripheral actions—both of which contribute to the therapeutic results obtained.

—Samples and literature upon request.—

All products bearing the VANPELT & BROWN label are processed in our own plant and guarded for quality and uniformity by rigid laboratory control.

VANPELT & BROWN, Inc.

Manufacturing Pharmaceutical Chemists

RICHMOND VIRGINIA

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

Complete list of members in active service as of October 1, 1943

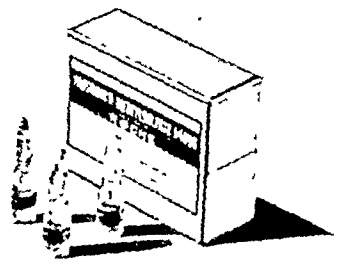
DR. GEORGE S. BERGH—(Major) M.C., 2420 West 24th Street, Minneapolis, Minnesota
DR. JOSEPH BANK
DR. H. R. BUTT—(Lt.) M.C.-V(S), U.S.N.R., % Naval Hospital, Corona, California
DR. JAMES L. BORLAND—(Maj.) M.C., 0-441695, 105th General Hospital, A.P.O. 923, % Postmaster, San Francisco, California
DR. DONALD T. CHAMBERLIN—(Major), 306th Stat. Hosp., Camp McCoy, Wisc.
DR. MANFRED KRAEMER—(Major), Station Hospital, Jefferson Barracks, Missouri
DR. LEWIS K. FERGUSON
DR. T. T. MACKIE—(Lt. Col.), Army Medical Center, Washington, D. C.
DR. SAMUEL OVERSTREET
DR. ALBERT M. SNELL—(Comdr.), M.C.-V(S), U.S.N.R. Tryon, % Postmaster, San Francisco, California
DR. JOHN L. KANTOR—(Col.), Headquarters 49th General Hospital, Borden General Hospital, Chickasha, Oklahoma
DR. D. B. FAUST, % D. E. Crandall, 1810 F Street, Vancouver, Washington
DR. SAMUEL MORRISON—(Major), Valley Forge General Hospital, Phoenixville, Pa.
DR. JOHN R. TWISS—(Comdr.) M.C., U.S.N.R.
DR. FRANK MEYERS—(Major), Base Hospital GH23, Fort Meade, Maryland
DR. P. M. GLENN—(Capt.) M.C., Finney General Hospital, Thomasville, Georgia
DR. P. W. BROWN—(Major) M.C., 89th General Hospital, Charleston, South Carolina
DR. B. D. ROSENAK—(Capt.) 0-460250, U. S. Army, 49th Stat. Hosp., APO 875, New York City
DR. JOHN H. WILLARD, 232 Jefferson Street, E. Greenville, Pennsylvania
DR. ALBERT J. SULLIVAN—(Major), Army Air Force, Station Hospital, Miami Beach, Florida
DR. DWIGHT L. WILBUR—U.S.N.R., U.S. Naval Hospital, Oakland, California
DR. CHARLES A. FLOOD, 410 Riverside Drive, New York, New York
DR. ROBERT ZOLLINGER, Peter Bent Brigham Hospital, Boston, Mass.
DR. C. W. WIRTS—(Capt.) M.C., 2017 Delancey Street, Philadelphia, Pa.
DR. THOMAS A. JOHNSON
DR. Z. TAYLOR BERCOVITZ—(Major) M.C., 0209820, A.P.O., % Postmaster, New York, New York
DR. DAVID H. ROSENBERG—(Lt. Comdr.) U.S.N.R., 310 South Michigan Avenue, Chicago, Ill.

—POSTOPERATIVE DISTRESS may mar the clinical picture to a discouraging degree. Abdominal distention and urinary retention, following surgery, are frequently the cause of complications necessitating troublesome procedures that are apt to retard the patient's recovery. The routine use of Prostigmin Methylsulfate* 1:4000 provides a convenient and effective means of preventing intestinal and bladder atony, minimizing the likelihood of "gas pains" and the need for catheterization. Try Prostigmin 'Roche' for a smoother, uninterrupted convalescence. Inject 1 cc (1:4000 solution) at the time of operation. Follow with 5 similar 1-cc injections at 2-hour intervals after the operation. HOFFMANN-LA ROCHE, INC. • ROCHE PARK • NUTLEY, N. J.

*Dimethyl carbamic ester of m oxyphenyl trimethyl ammonium methylsulfate

PROSTIGMIN 'ROCHE'

"FIGHT INFANTILE PARALYSIS • JANUARY 14th—31st"



If the hat fits . . .

If you are sometimes guilty of improper eating—and many physicians are simply because they cannot take the time to eat correctly—you can readily understand why millions of busy laymen in this country today run the constant danger of subclinical vitamin deficiencies. Unlike you, the average person has only a *fair* knowledge of proper nutrition. In spite of the present educational program, many people are too busy—too busy making planes, tanks, guns and other wartime essentials—to give but a passing thought to selecting the necessary foods for maintaining optimum health. They find it more convenient to select only those foods which can be speedily prepared and eaten. ● When physicians suspect that subclinical vitamin deficiencies do exist, they not only correct the unbalanced diet . . . but also, to make certain that optimum amounts of the important vitamins are received *daily*, they prescribe a dependable vitamin preparation as a supplementary measure. Many specify *Abbott* on their prescriptions. An Abbott vitamin preparation to them means *dependable* quality and potency. Why not be certain of this dependability . . . and also specify *Abbott?* ABBOTT LABORATORIES, North Chicago, Illinois.

Abbott
Vitamin Products

"See what a change . . . AFTER ONLY 10 DAYS!"

TEN DAYS after establishment of an ulcer regime with Amphojel, x-ray re-examination often reveals complete disappearance of the peptic ulcer niche.†

In addition to promoting rapid healing of the ulcer, Amphojel offers:

Prompt relief from pain . . .
Fewer recurrences . . .
Superior weight gain during treatment . . .
No alkalosis.

A Wyethical in 12 fl. oz. bottles. John Wyeth & Brother, Division WYETH Incorporated, Philadelphia.

†WOLDMAN, E. E., and POLAN, C. G.: The Value of Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer; A Review of 507 Consecutive Cases, Am. J. M. Sc. *198:* 155-164 (Aug.) 1939.

AMPHOJEL*
Wyeth's
ALUMINA GEL
*REG. U. S. PAT. OFF.

Entered as second-class matter February 3, 1940, at the postoffice at Baltimore, Maryland, under the Act of March 3, 1879.
Subscription price, $3.00 per volume. Single numbers 50 cents.

In gastric and duodenal ulcer...

PABLUM

as a palatable cereal food of high nutritional value has the following advantages: (1) rich in iron and calcium; (2) a good source of the vitamin B complex; (3) low fiber content and (4) convenience.

Pablum is convenient because it requires no cooking. Thus, the patient can prepare his meal at the office or shop simply by adding milk at any temperature. Pablum absorbs about 12 times its own weight of milk, so that it offers a good vehicle for milk.

In ulcerative colitis and intestinal tuberculosis, Pablum has also been found useful in the dietary.

Composition of Pablum

Wheatmeal (farina)	52%
Oatmeal	18
Wheat Germ	15
Cornmeal	10
Powdered Beef Bone (Specially prepared for human use)	2
Sodium chloride	1
Alfalfa Leaf	1
Dried Brewers Yeast	1
Reduced iron (11 Gm. per 100 lbs.)	

Approximate Analysis of Pablum

Carbohydrate (by difference)	69.9%
Protein (N X 6.25)	15.0
Moisture	7.0
Minerals (ash)*	4.2
Fat (ether extract)	3.0
Crude Fiber	0.9
*Including:	
Calcium	0.78%
Phosphorus	0.62
Iron	0.03
Copper	0.0013

Approximately 106 Calories per oz. or 3.7 per Gm. 12 level tablespoonfuls = 1 oz.
Each ounce contains not less than 0.3 mg. thiamine (vitamin B_1) and 0.1 mg. riboflavin (vitamin G).

MEAD JOHNSON & COMPANY, EVANSVILLE, INDIANA, U.S.A.

Please enclose professional card when requesting samples of Mead Johnson products to cooperate in preventing their reaching unauthorized persons.

FOR Smoother
EASING OF
SMOOTH MUSCLE SPASM
DONNATAL®
in

Pylorospasm
Hyperchlorhydria
Intestinal irritability
Biliary and renal colic
Dysmenorrhea
Enuresis
Parkinson's Disease
Vomiting of Pregnancy
—and other
manifestations

—affords all the advantages of natural belladonna alkaloids
YET IS SIGNIFICANTLY NON-TOXIC

—provides for effective sedation as well
YET IS ENTIRELY NON-NARCOTIC

—has marked pharmacologic potency
YET COSTS LESS

Donnatal provides the sedative action of phenobarbital, in addition to the superior spasmolytic influence of accurately predetermined quantities of belladonna alkaloids —judiciously proportioned to minimize the toxic reactions typical of atropine alone. It costs about half as much as synthetic preparations — less even than tincture of belladonna and elixir of phenobarbital. Patients find its tablet form particularly convenient.

Formula: Each tablet contains belladonna alkaloids (hyoscyamine, atropine, and scopolamine) equivalent to approximately 5 min. tr. belladonna; plus ¼ gr. phenobarbital.

Available: in bottles of 100 tablets.

THE DEPENDABLE
ANTI-SPASMODIC
AND SEDATIVE
Write for full details

A. H. ROBINS CO., INC. • RICHMOND, VA.

VOLUME 2, NUMBER 2 FEBRUARY, 1944

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

TABLE OF CONTENTS

VOLUME 11, NUMBER 1

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

WALTER C. ALVAREZ, *Editor*

A. C. IVY, *Assistant Editor*

ASSOCIATE EDITORS AND THEIR SUBJECTS

A. H. Aaron, *Technical Matters*
J. A. Bargen, *Large Intestine*
H. L. Bockus, *Liver and Gall Bladder*
W. C. Boeck, *Parasitology*
B. B. Crohn, *Small Intestine*
Robert Elman, *Pancreas*
Franklin Hollander, *Abstracts**
Sara M. Jordan, *Stomach*
J. L. Kantor, *Military Gastroenterology*
B. R. Kirklin, *Radiology*
Paul Klemperer, *Pathology*
F. H. Lahey, *Surgery*
F. C. Mann, *Physiology*
H. J. Moersch, *Esophagus*
V. C. Myers, *Biochemistry*
W. L. Palmer, *Stomach*
J. M. Ruffin, *General Reference*
Rudolf Schindler, *Gastroscopy*
D. L. Wilbur, *Nutrition*

*Assisted by a staff of 30 abstractors

EDITORIAL COUNCIL

IRVIN ABELL
A. F. R. ANDRESEN
LLOYD ARNOLD
B. P. BABKIN
C. J. BARBORKA
W. A. BASTEDO
E. B. BENEDICT
A. A. BERG
J. M. BLACKFORD
LEON BLOCK
R. S. BOLES
J. L. BORELAND
R. C. BROWN
T. R. BROWN
J. T. CASE
L. G. COLE
E. N. COLLINS
G. R. COWGILL
C. W. DOWDEN
L. R. DRAGSTEDT
E. S. EMERY, JR.
G. B. EUSTERMAN
J. H. FITZGIBBON
E. B. FREEMAN
E. H. GAITHER
L. C. GATEWOOD
F. D. GORHAM
R. H. M. HARDISTY
SEALE HARRIS
C. G. HEYD
A. A. JONES
C. M. JONES
C. R. JONES
N. W. JONES
J. W. LARIMORE
J. M. LYNCH
B. B. V. LYON
T. T. MACKIE
LAY MARTIN
J. G. MATEER
T. G. MILLER
W. G. MORGAN
H. NECHELES
MOSES PAULSON
G. M. PIERSOL
J. T. PILCHER
M. M. PORTIS
J. P. QUIGLEY
MARTIN REHFUSS
V. C. ROWLAND
ADOLPH SACHS
LEON SCHIFF
H. F. SHATTUCK
D. N. SILVERMAN
V. E. SIMPSON
A. M. SNELL
W. H. STEWART
H. M. SOPER
J. E. THOMAS
E. J. VAN LIERE
M. G. VORHAUS
F. W. WHITE

Published by

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, MD.

(In writing to advertisers, please mention the journal—it helps.)

MERCK QUALITY

IS A RECOGNIZED STANDARD FOR PURE VITAMINS

Merck Quality has come to be recognized as a standard of comparison for pure vitamins, for there is no standard of quality higher than *Merck Quality*.

Behind this rigidly maintained standard lies a long and rich experience in the vitamin field. Ever since the first of the pure vitamins was synthesized, the name Merck has been identified with leadership in the discovery, development, and production of these important therapeutic and nutritional substances.

Several pure vitamins were first synthesized in the Merck Research Laboratories; others have been synthesized for the first time by Merck chemists and their collaborators in other laboratories. The many discoveries and advances made by Merck chemists and their collaborators have repeatedly emphasized the outstanding rôle of Merck & Co., Inc. in vitamin research and production.

But *Merck Quality* is not only the result of pioneering experience. Constant laboratory control, with repeated checks and analytical tests, ensure the superb quality of every vitamin product bearing the Merck label.

MERCK & CO., Inc. *Manufacturing Chemists* RAHWAY, N. J.

(In writing to advertisers, please mention the journal—it helps.)

WAR-ENGENDERED food shortages may render the dietary of a large segment of our population deficient in proteins and B-vitamins. VioBin presents a unique means of bringing such deficient diets to optimum nutritional levels.

It is the richest of all protein foods, containing 40% of protein which, though of plant origin, is equal in biologic value to the proteins from animal sources, able to maintain optimum growth rate in experimental animals,[1] and to complement biologically inferior proteins as efficiently as those of animal origin.[2]

VioBin is an excellent natural source of the vitamins of the B-complex. One ounce provides the total minimum daily requirement of thiamine, and a goodly portion of that of the other B-complex components. It is also a rich source of iron and phosphorus.

Because of its high stores of these essential nutrients, its low fat content (0.85%), its high quotient of digestibility, and because it is thoroughly bland (chemically as well as mechanically), VioBin deserves consideration in the specialized diets called for by many pathologic conditions, and when nutritional deficiencies must be corrected or prevented; it may also advantageously supplement the diet in skin disorders in which dietary deficiencies are suspected.[3]

VioBin, defatted, partially dehydrated wheat embryo, yields only 3.5 calories per gram; it is dependably stable, and requires no refrigeration. *** The VioBin Corporation, Monticello, Illinois.

[1]Chick, H. Biologic Value of the Proteins Contained in Wheat Flours, Lancet 1:403 (April 4) 1942.
[2]J.A.M.A., Editorial, Sept. 12, 1942.
[3]Gross, P., and Kesten, B.: Treatment of Psoriasis with Lipotropic Substances from Foodstuffs, Arch. Dermat. & Syph. 47:159 (Feb.) 1943.

VioBin

Analysis %		Minerals IN ASH		Vitamins PER GRAM	
[illegible]	7.0%	Potassium as K	1.1 [illegible]%	Thiamine	33 gamma
[illegible]	93.0%	Calcium as Ca	0.067 [illegible]%	Riboflavin	8 gamma
[illegible]	2.3.0 [illegible]	Magnesium as Mg	0.353 [illegible]%	Nicotinic acid	69 gamma
[illegible]	2.0 [illegible]	Phosphorus as P	1.190 [illegible]%	Pyridoxine	15 gamma
[illegible]	4[illegible]15%	Manganese as Mn	0.009 [illegible]%	Pantothenic acid	35 gamma
[illegible]	[illegible]	Copper as Cu	0.00[illegible]%	Inositol	2.5 mg
[illegible]	5.0 [illegible]	Iron as Fe	0.011 [illegible]%	Biotin	452 [illegible] gamma

[illegible]

Pilate Washing His Hands—Rembrandt Courtesy Metropolitan Museum of Art

Masterpieces

ARE NOT CREATED EVERY DAY

Masterpieces are not created daily . . . years may elapse before one appears . . . then a school of painting may be started. So it has been with IODEIKON* N.N.R. First manufactured and distributed to the medical profession almost twenty years ago following the classic research by Graham, Cole, Copher and Moore on the x-ray visualization of the gall bladder and still produced and distributed by Mallinckrodt.

Further continuation of the research in the field of Cholecystography has developed the interesting fact that the isomer of IODEIKON,* (Iodophthalein Soluble U.S.P. XII) namely ISO-IODEIKON,* (Phentetiothalein Sodium N.N.R.) is capable of performing a two-fold function with a single injection of 2.5 grams of the dye . . . x-ray visualization of the gall bladder . . . test of the liver function.

Detailed technique and literature upon request.

*Trade Mark Reg. U. S. Pat. Off.

FINE CHEMICALS Mallinckrodt SINCE 1867

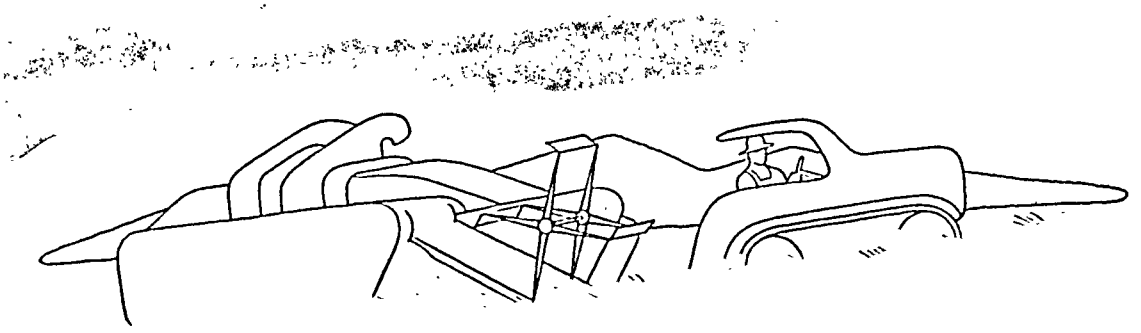
MALLINCKRODT CHEMICAL WORKS

77 Years of Service to Chemical Users

Mallinckrodt St., St. Louis 7, Mo. · 74 Gold St., New York 7, N. Y.

CHICAGO • PHILADELPHIA • LOS ANGELES • MONTREAL

FOR VICTORY BUY UNITED STATES WAR BONDS STAMPS



"On the whole," says Carlson†, "we can trust Nature further than the chemist and his synthetic vitamins."

The nutritional response obtained with *natural* Vitamin B Complex therapy cannot be duplicated by any combination of synthetic vitamins, according to investigators.

BEZON depends on Nature for its components—it is *Whole Natural* Vitamin B Complex, concentrated to high potency from natural sources —no synthetic vitamin factors are added. Only *Whole Natural* Vitamin B Complex contains *all 22* B vitamins. In prescribing BEZON, the entire Vitamin B Complex is assured —an important fact inasmuch as Vitamin B deficiencies tend to be multiple.

BEZON is the only *Whole Natural* Vitamin B Complex which contains one milligram of natural thiamine, two milligrams of natural riboflavin, together with all the remaining members of the B complex, concentrated in one capsule or two tabules.

Supplied in bottles of 30 and 100 capsules; 60 and 200 tabules.

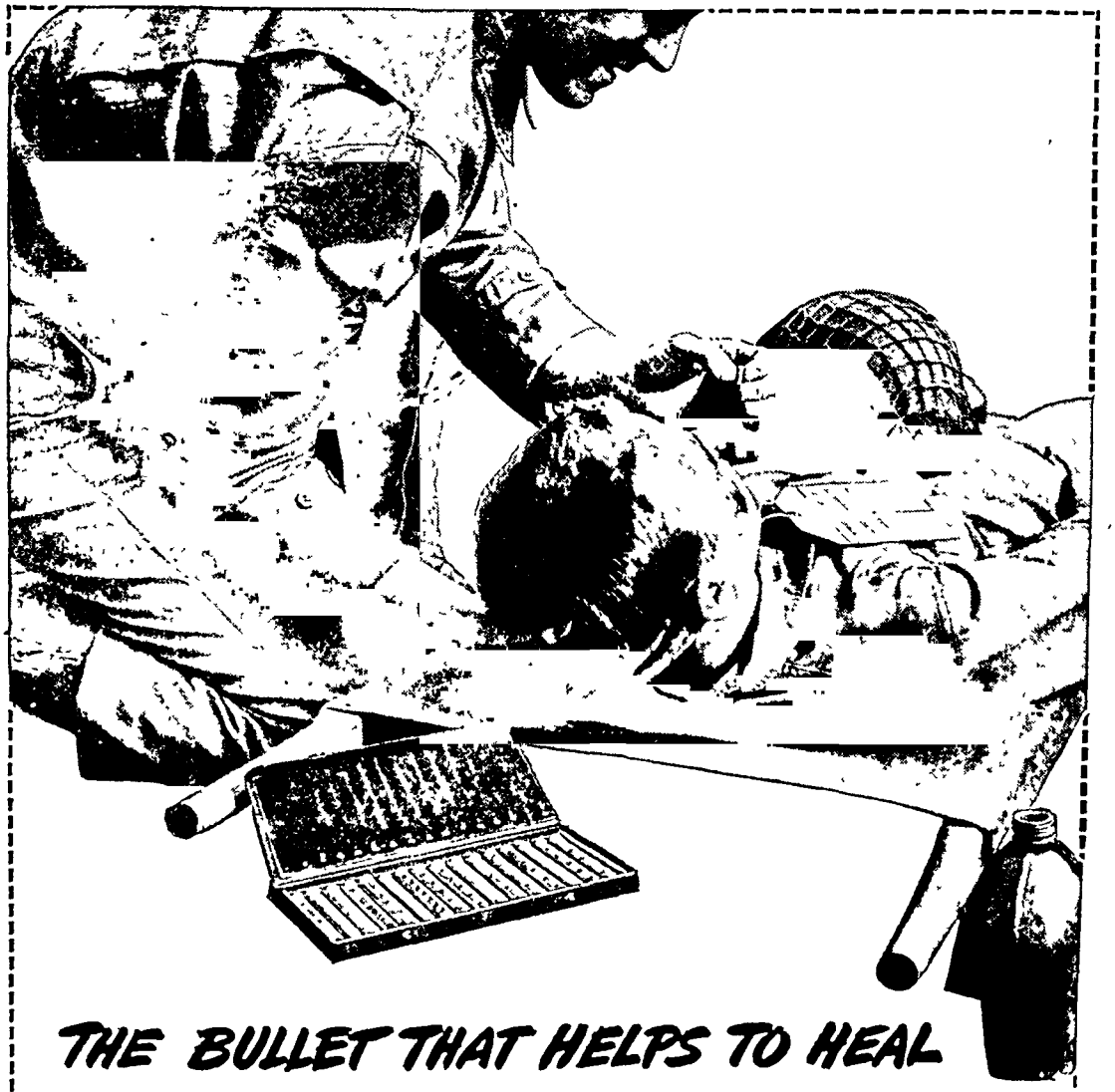
Samples and literature available on request

†Carlson, A. J., Science, 97, April 30 and May 7, 1943

*Trade Mark

NUTRITION RESEARCH LABORATORIES • CHICAGO

whole natural
VITAMIN B COMPLEX



THE BULLET THAT HELPS TO HEAL

Our men call it the "green bullet." Shining green, it's as swift to solace as the deadly kind is to strike.

When a man's wounded, the "green bullet" is administered along with first aid. Gently it lets him slip off into sleep, cushioning his nerves against the shock of injury until he can be moved to the base hospital, where physical recovery can begin, unhindered by scars of the mind.

Making gelatine for the capsules that hold this green bullet and other pharmaceuticals is one of the war jobs being done by the makers of Knox. Another is the manufacture of gelatine for such special uses as X-raying metal castings...blue printing... map-making...aerial photography of camouflage.

The makers of Knox are able to meet these exacting specifications through rigidly controlled manufacturing processes and close laboratory supervision. These are the same methods that have made Knox Gelatine a standard of purity and quality for more than a half-century.

KNOX GELATINE Johnstown, New York

(In writing to advertisers, please mention the journal—it helps.)

In Peptic Ulcer . . .
Hyperacidity . . .
Gastritis . . .

Magmasil

Greater Acid Neutralizing Power

•

Longer Protective Action

•

Fewer Doses Needed

•

No Constipation

A stable aqueous suspension of hydrated magnesium trisilicate in extremely fine subdivision, Magmasil is an outstanding advancement in the treatment of peptic ulcer, gastritis, hyperchlorhydria.

Its antacid action is powerful; one teaspoonful neutralizes 86 cc. of N/10 HCl. It is prolonged, extending over fully four hours.

Hence fewer doses are needed, the customary 11 P.M. administration usually holding the patient comfortable through the night.

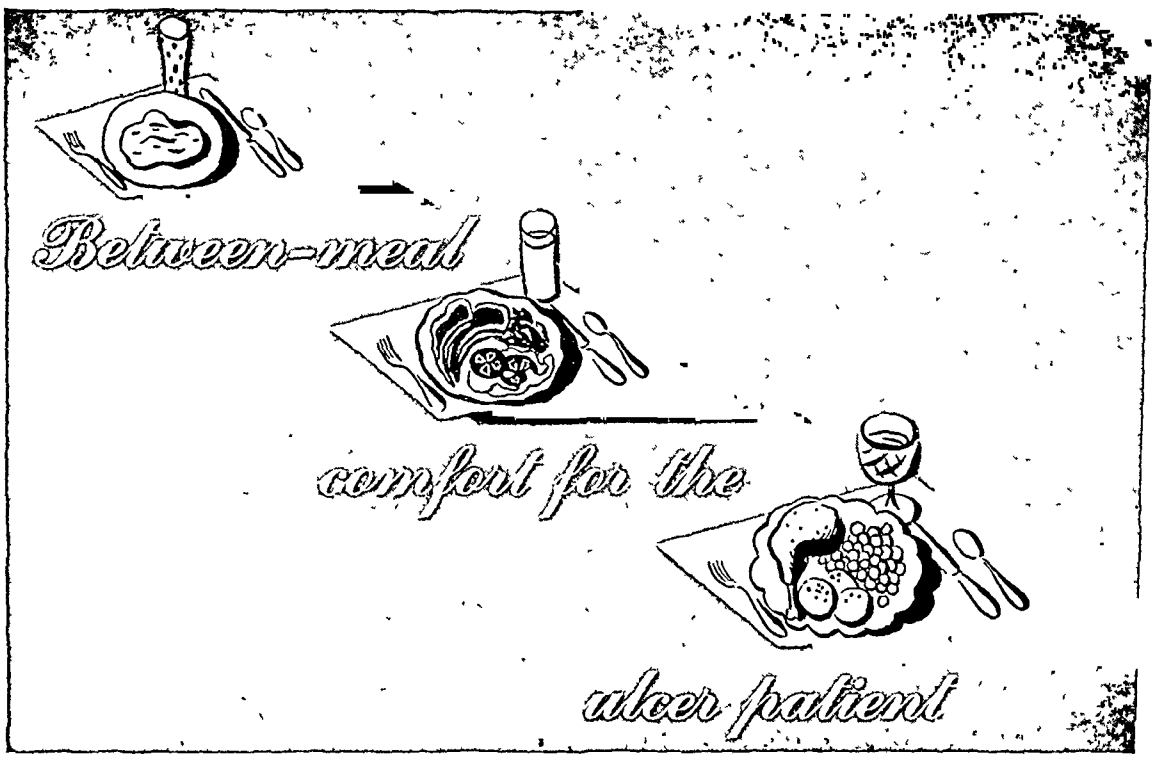
Magmasil is free from the drawbacks and limitations of many other antacids. There is no alkalosis, no chloride depletion, no undesirable astringency, no constipation which has made the patient uncooperative with other methods.

Pain and pyrosis are stopped promptly, and healing is brought about rapidly.

THOS. LEEMING & CO., INC. 155 E. 44th St. New York 17, N.Y.

Magmasil is available through all pharmacies in 12 oz bottles.

Physicians are invited to send for samples and a complimentary copy of the brochure "Twenty Years of Progress in Ulcer Therapy."



An unbroken cycle of comfort is the goal of the "continuing" action of Malcogel.* Throughout the trying between-meal period Malcogel's combination of acid-neutralizing magnesium trisilicate with rapidly acting aluminum hydroxide helps to free the patient from gastric distress.

Relief with Malcogel is distinguished by the absence of many faults inherent in earlier forms of therapy.

Malcogel does not produce an acid rebound
Malcogel does not cause alkalosis
Malcogel has less constipating tendency than simple alumina therapy

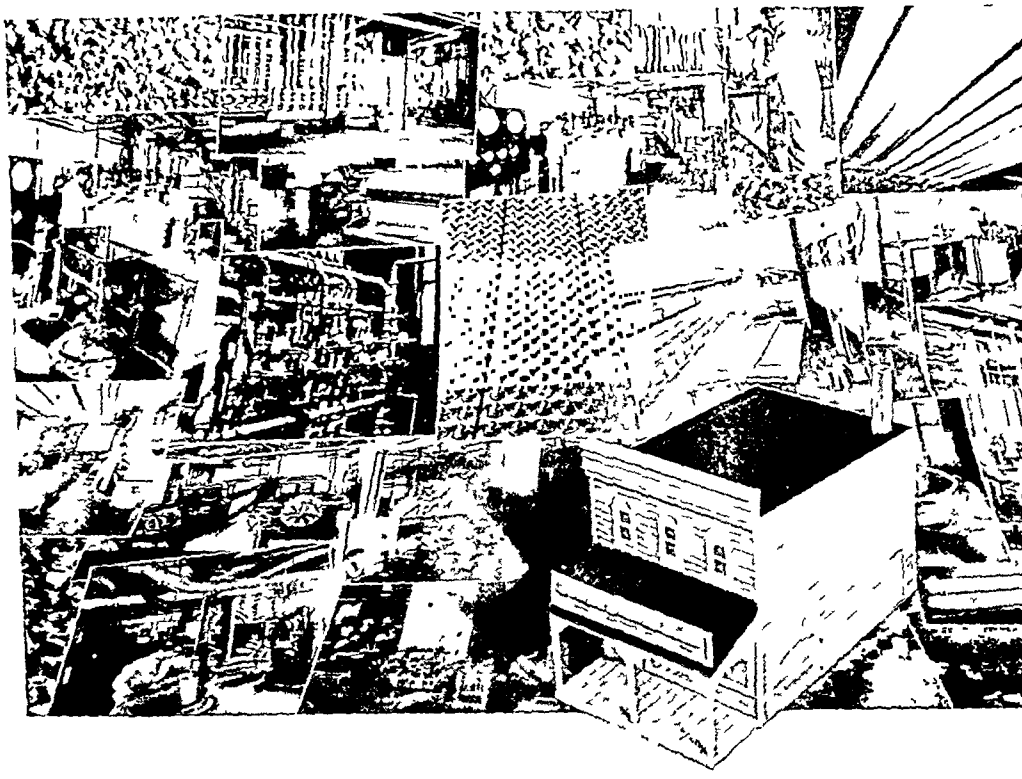
Pleasantly and simply Malcogel's prolonged action protects and soothes the injured muco-a to achieve an unbroken cycle of comfort and an early rehabilitation of the patient. *Trademark

MALCOGEL

a palatable suspension, each ounce containing 7.5 0 grains of magnesium trisilicate and 17.5 grains of aluminum hydroxide. Supplied in bottles of 12 oz

Upjohn
KALAMAZOO, MICHIGAN

NEUTRALIZE THE AXIS — BUY MORE WAR BONDS



WILLIAM JONES, PH.G.

WHEN THE DOORS of the Jones Pharmacy opened for business many years ago, young Mr. Jones, then just out of pharmacy school, had some definite ideas about the manner in which a prescription department should be conducted. He knew all about fresh crude drugs, and he could triturate, macerate, and percolate with the best of them. He provided sparkling glassware, and his finished prescriptions were things of beauty. He operated very successfully and the doctors liked to have him do their compounding.

Things have changed since that day when Mr. Jones opened his store. For example, along about 1923 quite a commotion was raised over something called Insulin, discovered by a couple of fellows up north. Mr. Jones immediately established an Insulin department. He was quick to realize, however, that the tons of equipment required for grinding pancreas glands and processing them through a complicated series of extractions, concentrations, and purifications had no place in his store. Mr. Jones's Insulin is manufactured in Indianapolis, miles and miles away.

The production and standardization of Iletin (Insulin, Lilly) in its various strengths and modifications is but one of the many contributions Eli Lilly and Company has made toward the improvement of Pharmacist Jones's service to the medical profession.

BUY WAR BONDS

Lilly ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U. S. A.

injectable vitamin B complex!

THE FIVE IMPORTANT FACTORS IN STABLE

Instantly Soluble FORM

As a result of chemical investigations still further progress in vitamin therapy has been made. Now, in one ampul, there are available the following synthetic factors:

Thiamine hydrochloride (vitamin B_1)...10 mg.
Riboflavin (vitamin B_2)..... 5 mg.
Pyridoxine hydrochloride (vitamin B_6). 5 mg.
Calcium pantothenate..... 5 mg.
Niacinamide (nicotinic acid amide)....50 mg.

Supplied in boxes of 3 and 10 ampuls.

Dissolve in 2 cc. of sterile distilled water.

If increased vitamin B_1 is desired, use as solvent any Betaxin parenteral solution (available in 10 cc. vials containing in each 1 cc. either 10 mg., or 25 mg., or 50 mg., or 100 mg.).

Betasynplex may be administered

subcutaneously
intramuscularly
intravenously

BETASYNPLEX "NIPHANOID"*
Reg U S Pat Off & Canada

Winthrop
CHEMICAL COMPANY, INC.
Pharmaceuticals of merit for the physician NEW YORK, N. Y. • WINDSOR, ONT.

* "Niphanoid," trademark, Winthrop Chemical Company, Inc

No Confusion...

..Only *one type* ZymenoL

Equally Effective in CONSTIPATION-COLITIS-DIARRHEA

Different types or combinations are not needed because ZymenoL is a *Natural Approach* to the two basic problems of Gastro-Intestinal Dysfunction:

NORMAL INTESTINAL CONTENT ASSURED
..Through Brewers Yeast Enzymatic Action.*

NORMAL INTESTINAL MOTILITY RESTORED
..With Complete Natural Vitamin B Complex *

This two-fold natural therapy restores normal bowel function without catharsis, artificial bulkage or mineral oil leakage.

Teaspoon Dosage Economical Sugar Free

Write for Free Clinical Size

*ZymenoL Contains Pure Aqueous Brewers Yeast (no live cells)

OTIS E. GLIDDEN & COMPANY, INC. EVANSTON, ILLINOIS

(In writing to advertisers, please mention the journal—it helps.)

IN LABORATORY ANIMALS, response to B-vitamin therapies discloses these facts:

1. Completely satisfactory results are *not* obtainable with individual crystalline vitamins or synthetic mixtures.
2. Fully effective results follow the use of *natural* vitamin B complex.

Clinical results concur, when the supplement employed is Elixir B-Plex—the *natural* vitamin B complex.

A Wyethical available in 8 fl. oz. bottles.

John Wyeth and Brother, Division WYETH Incorporated, Philadelphia

ELIXIR B-PLEX *Wyeth's* THE NATURAL VITAMIN B COMPLEX

GASTRITIS IN THE MILITARY SERVICE[1]

J. W. Annis, Major, M.C.

INTRODUCTION

The importance of chronic dyspepsia in modern warfare is well established. Its actual incidence, however, is not too well established to bear closer investigation, and while that is not the purpose of this paper, the subject under discussion is illustrative of the point. One need only examine Dunn's (1) review of the current literature on the subject to be impressed by the complete disorder of available statistics and the equally complete lack of rigid diagnostic criteria employed. This is particularly true of the British figures concerning gastritis, which refer generally to a loosely knit group of cases related solely through vague clinical impressions without gastroscopic confirmation. This has already been emphasized by Hurst (2) and Gold (3).

The need for more factual evidence on gastritis is great—the opportunity for collecting these data in the armed services is even greater. The importance of such recorded data lies in two factors. The first, and lesser, is the tremendous problem which this condition must invariably represent in future pension rolls. The second and more important is the opportunity and duty which we have of recording all our findings even though they may seem of academic interest only at the present. This should be done to the end that they may at some future date supply a more correct and specific answer to some aspect of a much discussed problem. Just as in electrocardiography and roentgenology, observation and notation must long precede full and correct interpretation. It is as puerile to adopt the attitude that because the exact significance of observed physical change is not understood—that such a change is unimportant—as it is to assume that every variation noted is per se the cause of all the patient's complaints.

To return to the practical aspect of the situation, the Army asks of us three questions: (1) What is the frequency of gastritis? (2) Who shall be gastroscoped and what is the magnitude and the importance of this task? (3) What shall be the disposition of these cases?

With these problems in mind I have attempted to evaluate carefully those patients gastroscoped at the Station Hospital, Camp Blanding, Florida, during the past two years, feeling that since our figures represent all the hospital admissions of a given command they will produce a true cross-section of the incidence of any condition in our troops.

[1]Read before the Regional Meeting of The American College of Physicians, Jacksonville, Florida, Wednesday, May 26, 1943.

Present location: Station Hospital, Camp Blanding, Florida.

MATERIAL

Of the total hospital admissions during this period, 2,755, or approximately 11% of the total medical patients, were admitted to the Gastro-Intestinal Service. This figure includes 613 patients with epidemic jaundice following inoculation, who have been excluded hereafter for statistical purposes in order to produce a more correct representation of the true incidence of various disease entities. After this exclusion there remain 2,142 Gastro-Intestinal patients. This does not include an approximately equal number of out-patient visits.

It goes without saying, I believe, that the clinical diagnosis of gastritis should be made only from gastroscopy. For the basis of this study all cases of gastric ulcer, tumor, trichophytobezoar, anomalies, etc., have been eliminated and only those chronic dyspeptics who presented solely some form of gastritis or whose gastroscopic examination was entirely normal were considered. These patients number 276 and the individual examinations 286.

FINDINGS

What is the frequency of gastritis? One hundred sixty-seven were gastroscopically normal while 109 or 39.5% showed some form of gastritis. Of these cases, 52 showed hypertrophic changes, 44 superficial changes, and 13 atrophic changes. The age range was from 18 to 57 years, the majority, naturally, falling in the third decade. These 109 cases represent then roughly 5% of all admissions to a large and active service where many temporary and acute conditions exist. As such, the statistical importance of gastritis is readily apparent. It is further to be emphasized that these figures are a conservative minimum since the number of examinations which could be done was limited by the facilities at hand and by the volume of other work to be carried out on the service. These made the selection of cases rigid and undoubtedly allowed many cases to be overlooked, particularly if some other pathology was present.

This raises the second question; that is, who in the Army shall be gastroscoped? Ideally, of course, the answer is simple; i.e., all chronic dyspeptics without other organic findings which adequately explain their symptom complex. This would be a considerable task—yet I feel that were it possible we might be amply repaid. Practically, this is a different matter for the busy gastroenterologist with a large number of patients to care for and re-evaluate for duty. For this reason a careful and detailed tabulation was made of the character, location and duration of symptoms involved, as well as of the physical characteristics of the patient, his age, habits, nativity, family history, gastric analysis, X-ray findings, response to therapy, and associated diseases

TABLE I

Explanation	Normal	Hypertrophic Gastritis	Atrophic Gastritis	Superficial Gastritis
Number of cases	167	52	13	44
Symptoms and Characteristics—Percentage				
Pain	91.6	86.5	76.9	100.0
Type:*				
Burning	43.8	71.1	40.0	40.9
Gnawing-hunger	3.3	2.2		4.5
Vague	52.9	26.7	50.0	54.5
Sharp			10.0	
Location:*				
Epigastric	77.1	100.0	80.0	79.5
Diffuse	18.3	6.7	10.0	11.4
Periumbical	3.3			6.8
R.U.Q.	1.3	6.7		2.3
R.L.Q.	1.9			
L.U.Q.		6.7	10.0	
Anorexia	34.1	46.2	38.5	25.0
Nausea	59.3	71.2	61.5	68.2
Vomiting	44.9	55.8	46.5	52.3
Hematemesis	10.2	17.3	7.7	18.1
Melena	3.6	11.5	15.4	4.5
Weight Loss	27.5	32.7	30.8	29.5
Average amount	11.7 lb.	14.7 lb.	31.0 lb.	10.2 lb.
Periodicity	39.5	59.6	30.8	50.0
Pain-Food-Ease Sequence	25.1	40.4	15.4	31.8
Alkali relief	32.9	55.8	7.7	47.7
Post-prandial distress	48.5	44.2	46.5	38.5
Early satiety of Appetite	10.8	48.1	30.8	20.5
Duration of Symptoms	3.0 yr.	4.9 yr.	3.6 yr.	2.5 yr.
Ulcer diathesis	61.7	84.6	53.8	56.8
Family History of dyspepsia	22.2	26.9	15.4	29.5
Alcohol†				
None	42.0	40.4	14.3	23.8
Mild to moderate	54.9	55.3	71.4	73.8
Heavy	3.1	4.3	14.3	2.4
Smoking†				
None	19.8	16.7	11.1	15.9
Mild to moderate	72.2	39.6	44.4	77.3
Heavy	8.0	43.7	44.4	6.8

TABLE I—*Concluded*

Explanation	Normal	Hypertrophic gastritis	Atrophic gastritis	Superficial gastritis
Body Build				
Asthenic	24.8	30.0	33.3	25.0
Sthenic	73.3	70.0	58.3	70.5
Hypersthenic	1.8		8.3	4.5
Age				
Below 20	6.0	5.8	15.4	4.5
20-30	76.7	55.8	46.5	75.0
30-40	15.0	32.7	30.8	18.1
Over 40	2.4	5.8	7.7	2.3
Nationality	No significant distribution			
X-Ray Distribution of Gastritis	5.4	42.3		9.1
Free HCl (Fractional Test with Ewald or Alcohol Meals)				
None (With Histamine)	5.6	4.3	15.4	2.5
Normal	68.1	68.1	69.2	70.0
Marked-hyperchlorhydria (Free HCl Over 60)	26.4	27.7	15.4	28.5
Response to Therapy				
None	15.1	5.3		
Poor	32.5	23.7	40.0	22.7
Fair	31.9	55.3	40.0	34.1
Good	20.5	15.7	20.0	43.2
Associated Psychoneurosis	43.1	8.5	7.7	20.5
Nativity				
North	32.3	43.0	33.3	35.7
South	67.7	57.0	66.7	64.3

* Represents percentage of patients exhibiting this symptom.
† Represents percentage of patients exhibiting this habit.

in an effort to aid in selection of cases for examination. These are presented in Table I and, disappointingly enough, serve only to confirm in general the experiences of others as to the lack of importance of any one factor or group of factors in constituting a distinct clinical syndrome.

Dividing all cases gastroscoped into four groups—(1) normal, (2) hypertrophic gastritis, (3) atrophic gastritis, and (4) superficial gastritis—one finds that a comparison of the percentile value of the various factors studied in the different gastritides and in the normal appearing stomach, avails but little except in a few instances. The following facts seem important:

(a) There is a definite tendency toward the occurrence of a more or less typical clinical picture of ulcer in the hypertrophic group.

(b) Pain is the most frequent presenting complaint in all groups but its type and location are not characteristic in any.

(c) Nausea is the second most frequent complaint followed by vomiting as the third.

(d) History of anorexia, hematemesis, melena, weight loss, periodicity, post prandial distress, early satiety of appetite, and duration of symptoms are not informative.

(e) Alcohol and tobacco seem unimportant as etiological agents, although the incidence of heavy smokers was considerably greater among the group with hypertrophic and atrophic forms of gastritis than among the normals or among those patients with superficial gastritis.

(f) Body build, age, nationality, nativity, ulcer diathesis, gastric analysis and family history all ran approximately parallel in each group as did the clinical response to therapy.

(g) The X-ray indications of gastritis was of little or no value except in cases of severe hypertrophic gastritis, in which cases our roentgenologist was surprisingly accurate in his positive diagnoses when judged by the currently reported standards. His interpretation of this condition was based upon disruption of the mucosal pattern following compression, with breaks in the longitudinal folds, rather than upon any attempt at evaluation of the width of the rugal markings. Negatively, however, the results were less accurate.

Summary of the above facts renders it readily apparent that there is no definite clinical history which corresponds with the observed gastroscopic change. Yet I strongly suspect that a careful selection of cases may increase the percentage of gastritis seen by me as much as 50 or 100 per cent. It should be emphasized that in the above cases, gastritis was not necessarily the sole cause of all the symptoms presenting. The frequent occurrence of psychoneurosis, constitutional inadequacy, infestation with hookworm, irritable bowel syndrome, and other less common conditions serve to complicate the picture. In this regard, and as would, perhaps, be expected, true psychoneurosis was seen much more commonly in the chronic dyspeptic with a normal gastric mucosa and without organic findings than in any other group. In this connection the diagnosis of psychoneurosis was made by the psychiatrist, not the internist.

In the interpretation of these results there is an additional factor to be borne in mind; i.e., that to date our figures have dealt not with soldiers in active combat but with individuals in a transition stage between civilian and combatant. This group should in the future be separated from groups of

soldiers in actual warfare for the purpose of comparison and study. From the subsequent behaviour of patients in the former group we may learn much regarding the prognosis and proper disposition of future questionable cases. This again emphasizes the need for preservation of careful gastroscopic records from the standpoint of knowledge of the disease as well as from the standpoint of future claims and pensions. There is a recognized need for carefully studying gastroscopically normal individuals without dyspepsia, and certainly there is no better place to obtain this material than in the well controlled personnel of the Armed Services.

What is the present significance of finding gastritis in a patient, especially in a soldier? That this question is difficult to answer may be seen from the recently published symposium on the subject held at the last meeting of the American Gastroenterological Association (4). Certain facts seem, however, to be well established. In the first place we are dealing with an objective entity which at present we are unable to correlate satisfactorily with a clear-cut clinical picture.

Secondly, we must be careful in our manipulation and classification of this still somewhat nebulous subject in order to avoid the errors ever attendant upon impatience and haste. It is only natural that, encouraged by the great strides made possible by the flexible gastroscope, we should somewhat summarily demand full and complete knowledge of all its phases and cycles. We are apt to become intolerant of facts or trends which fail to fall into our preconceived mental picture of the subject and which seem for the moment to contradict our theories. At this stage in our consideration of gastritis we must be careful not to allow the natural sense of frustration to force us into hasty commitments solely on the basis of being unwilling to momentarily retard our progress. We must specifically be careful, it seems to me, not to overemphasize the psychogenic aspects of the situation simply because here none can say us nay. Psychosomatic manifestations are undoubtedly numerous and important in gastritis, but we should proceed with caution before placing them in the dominant role and abandoning a more organic basis for the observed gastroscopic change. Neither must we attribute all the vague general and abdominal distress of a constitutionally inadequate individual to minor variations in his gastric mucosa. We have learned this lesson too well and too recently in chronic cholecystitis and cholelithiasis to forget it pardonably here.

Agreeing that the present degree of significance of gastritis is in doubt, let us be careful not to say that it has little or no significance merely because the final truth continues temporarily to evade us. Since the symptoms of dyspepsia depend largely on the functional rather than the organic changes in the tract—as evidenced by the rapid disappearance of distress in such conditions as duodenal ulcer—it seems logical to assume that any anatomical change acts

merely as a stimulus or a trigger mechanism which unleashes the ensuing barrage of functional disorder. If such a functional upset has been hovering near a threshold level it is obvious that the exciting stimulus need be but slight. As has been frequently observed we are dealing with an individual not a symptom. What is equally important, but less adequately appreciated, is the fact that the individual is dynamic, not static, and that his clinical picture represents so to speak the vector of all operating functional and organic forces. These forces, of course, vary from day to day and for this reason no one of them should be arbitrarily convicted for their collective crimes.

Much more work on gastritis remains to be done at the present time and the continued careful recording to findings together with critical attempts at correlation of cause and effects are essential before the true import of the entity is established. We know that a patient may bleed to death from a previously asymptomatic and unsuspected peptic ulcer. Shall we then say that prior chance disclosure of that ulcer would have been unimportant? It is equal folly to assume that the definitely observed anatomical change of gastritis may be arbitrarily dismissed.

RESULTS OF THERAPY

The response of gastritis to treatment, which is at best indifferent even in civilian life, is certainly not likely to be satisfying in the care of the soldier with his less well controlled routine. When severe gastritis was present with marked symptoms, and with or without complication by other diseases, the results of my treatment were poor so long as the patient remained in the service. I have seen no soldier with severe symptoms accompanying a marked chronic gastritis who has done well in the Army, regardless of any change which has taken place in his gastroscopic picture.

Therapy has consisted of the generally accepted measures of lavage with silver nitrate, hydrogen peroxide, etc., high vitamin therapy, rest, reclassification, dietary measures, and in the atrophic form, adequate amounts of parentally administered liver. In only about twenty per cent of instances did I obtain what might be considered good results.

What shall be the disposition of these cases? The ineffectiveness of therapy leads automatically to the answer of the third question raised at the beginning of this paper; that is, the disposition of cases. From the practical aspect of the situation all patients with moderate or severe changes have been recommended for separation from the Service, and those with a mild disease have been reclassified and retained in less strenuous positions. Since dietary control is in no wise possible in the Army this latter solution has not been as effective as might be anticipated. These men have not made good soldiers as judged by actual trial at duty following hospital treatment.

I am in accord with the views of McGlone (5), Flood (6), and Chamberlain

(7), regarding the unfitness of patients with peptic ulcer for military service, and I am equally convinced that the patient with chronic gastritis is likely to be a military liability. Indeed, it is hard to think of a form of chronic dyspepsia, organic or functional, which does not prevent the individual from becoming an effective field soldier. This view is concurred in by Captain Seward of the Neuropsychiatric Section of our Medical Service. This Section, i.e. Neuropsychiatric, made all the diagnoses of psychoneurosis.

SUMMARY

The importance of gastritis in the military service has been reviewed from the standpoint of incidence, importance, and disposition of these cases, and a brief resume of the data in our series has been provided. Some of the factors influencing the course and symptomatology of the condition have been considered and an attempt has been made to evaluate the practical aspect of the situation as it applies to military medicine. On the basis of the above findings it is felt that the maintenance of equipment and personnel necessary for gastroscopy is both justifiable and expedient for every large army hospital with an active gastro-intestinal service.

BIBLIOGRAPHY

(1) Dunn, W. H.: War. Med., **2**: 967, 1942.
(2) Hurst, A.: Am. J. Dig. Dis., **8**: 321, 1941.
(3) Gold, Rubin L.: Gastroenterology, **1**: 254, 1943.
(4) *Symposium on Symptomatology of Chronic Gastritis*, Gastroenterology, **1**: 264 (March) 1943.
(5) McGlone, Frank B.: Gastroenterology, **1**: 258, 1943.
(6) Flood, Charles A.: War Med., **3**: 160, 1943.
(7) Chamberlain, Donald T.: Am. J. Dig. Dis., **9**: 245, 1942.

THE EFFECT OF SODIUM ALKYL SULFATE ON THE PEPTIC ACTIVITY OF THE GASTRIC CONTENTS AND ON THE HEALING OF GASTRIC ULCER IN MAN[1]

JOSEPH B. KIRSNER, M.D., PH.D., AND REGIS A. WOLFF, M.D.
From the Frank Billings Medical Clinic and Department of Medicine, University of Chicago

INTRODUCTION

Recent studies by Shoch and Fogelson (1) have demonstrated that sodium alkyl sulfate (2), a synthetic detergent of the anionic series, is capable of markedly inhibiting the peptic activity of gastric juice in vitro. This effect, in contrast to the action of such antacids as aluminum hydroxide, aluminum phosphate, magnesium trisilicate and calcium carbonate, is produced without significant deviation in pH from the acid range. A similar inhibition of peptic activity by this detergent was demonstrated in vivo (3) and greatly increased the survival time of dogs with ulcers induced experimentally by the massive histamine injection technique of Code, Wangensteen and others (4, 5). Fogelson and Shoch (6) recently have described favorable clinical results in previously refractory cases of peptic ulcer following the use of sodium alkyl sulfate. In view of these observations a study was undertaken to determine (A) the effect of sodium alkyl sulfate on the peptic activity of the gastric contents in man and (B) the effect of sodium alkyl sulfate on the clinical course of four patients with chronic gastric ulcer.

EFFECT OF SODIUM ALKYL SULFATE ON PEPTIC ACTIVITY

A. The action of sodium alkyl sulfate on peptic activity was first investigated in three adult male patients with duodenal ulcer. The gastric contents were partially aspirated every two hours from 8 a.m. to 8 p.m. The 8 a.m. sample served as a fasting control for each experiment. Control observations were obtained also during the administration of 90 cc. of an equal mixture of milk and cream at hourly intervals from 8:30 a.m. to 7:30 p.m. The experiments consisted in the administration of varying amounts of sodium alkyl sulfate every hour, together with the milk and cream. The detergent was given in capsules each being punctured at both ends before taken by the patient. The pH of the samples of gastric content was measured by the Beckman glass electrode. Peptic activity was determined by the Beazell (7, 8) modification of the Anson-Mirsky method (9); the procedure was further simplified and adapted for the Evelyn photoelectric colorimeter (10). The values are expressed as milliunits of peptic activity per cc. of gastric content. The results

[1] This study was supported in part by a grant from Abbott Laboratories, North Chicago, Ill.

for each patient are shown in figures 1, 2 and 3. It will be noted that sodium alkyl sulfate in doses of 130, 260, 390 or 520 mg. hourly did not produce a detectable lowering of peptic activity. No significant change occurred in the pH of the gastric content.

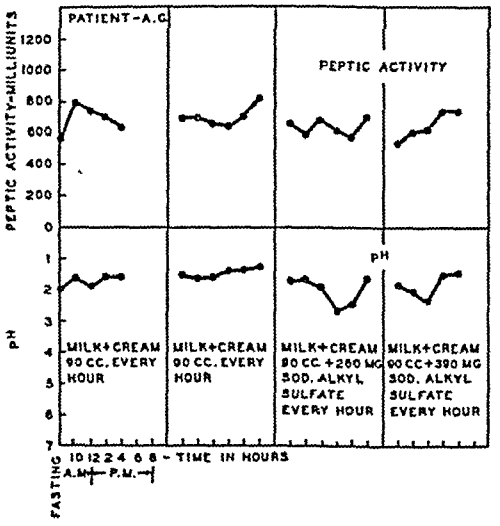


FIG. 1

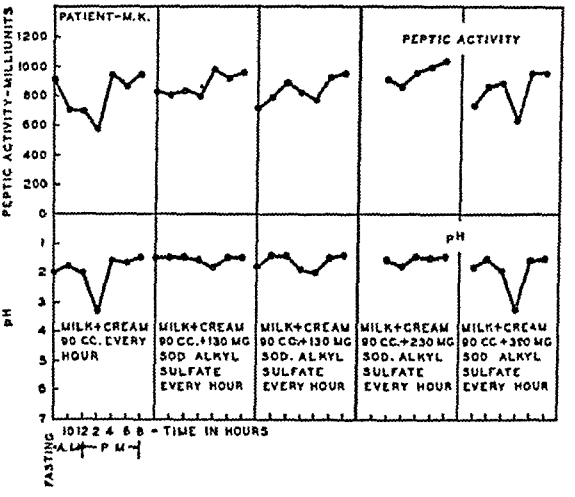


FIG. 2

FIG. 1. Effect of sodium alkyl sulfate on peptic activity and pH of gastric contents
FIG. 2. Effect of sodium alkyl sulfate on peptic activity and pH of gastric contents

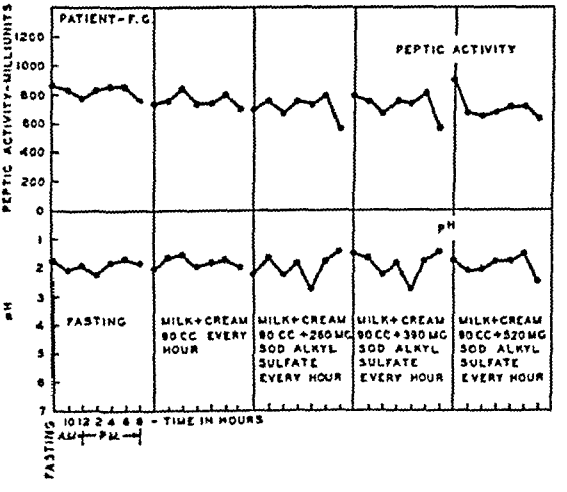


FIG. 3. Effect of sodium alkyl sulfate on peptic activity and pH of gastric contents

Inasmuch as a simultaneous study by us (11) disclosed that certain lipids were capable in vitro of retarding the inhibitory action of sodium alkyl sulfate on peptic activity, the possibility was considered that the lipids present in the milk and cream given the patients might have interfered with the action of the detergent in man. Accordingly, peptic activity was measured in three

adult male patients with duodenal ulcer during the use of a three meal diet estimated to be low in fat and during the use of the same diet together with sodium alkyl sulfate given in 780 mg. doses at hourly intervals from 8:30 a.m. to 5:30 p.m. As shown in figures 4, 5 and 6, the combination of sodium alkyl

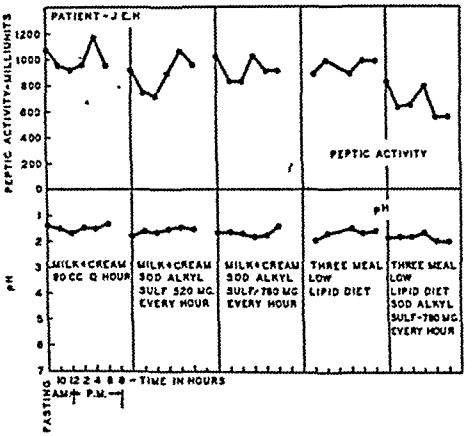


FIG. 4. Effect of sodium alkyl sulfate and low lipid diet on peptic activity and pH of gastric contents

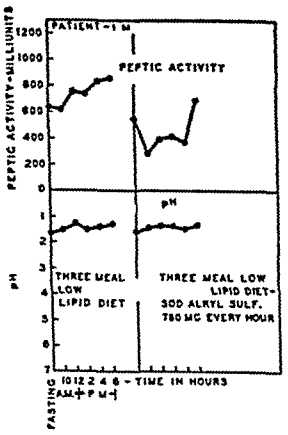


FIG. 5

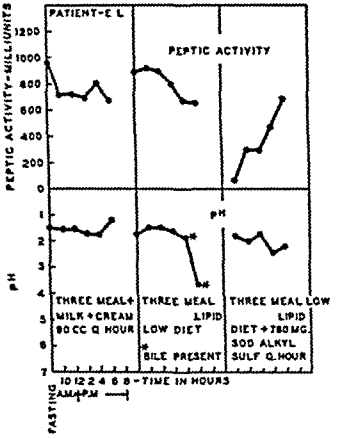


FIG. 6

FIG. 5. Effect of sodium alkyl sulfate and low lipid diet on peptic activity and pH of human gastric contents

FIG. 6. Effect of sodium alkyl sulfate and low lipid diet on peptic activity and pH of gastric contents

sulfate and the low fat diet produced an appreciable decrease in peptic activity. In patient I. M. the values diminished to between 276 and 406 milliunits. In patient E. L. peptic activity was lowered to 64 and 298 milliunits. This inhibitory effect was temporary and by 6 p.m. peptic activity had risen to levels

approximating control values. No apparent toxic effects resulted from the use of sodium alkyl sulfate in these experiments. A mild temporary diarrhea developed in one patient. The blood count, urine and serum bilirubin remained normal.

EFFECT OF SODIUM ALKYL SULFATE ON HEALING OF GASTRIC ULCER

B. The effect of sodium alkyl sulfate on the clinical course of peptic ulcer was studied in four patients with gastric ulcer. In each instance the ulcer was readily visualized by gastroscopy. The peptic activity and pH of the gastric contents were measured during the use of a low fat diet alone and together with sodium alkyl sulfate. Roentgen and gastroscopic examinations were made at various intervals during the experiment. The patients were carefully observed for the development of toxic manifestations. In addition, analyses were made frequently of the red and white blood cell counts, hemoglobin, differential blood smear, urine, serum bilirubin, cholesterol and cholesterol esters. Hepatic function was estimated by the intravenous hippuric acid test (12). The results are presented as individual case reports. The study is of particular interest in that the quantities of sodium alkyl sulfate used were enormous and, to our knowledge, much larger than have been administered heretofore to man.

Case 1. J. F. (Unit No. 173557) a 44 year old male had experienced ulcer distress periodically for fourteen years. Roentgen examination disclosed a huge ulcer crater on the lesser curvature of the stomach. At gastroscopy a very large, benign-appearing ulcer was seen on the anterior wall of the lesser curvature just above the angulus. The essential data are recorded in table 1. It will be noted that a definite decrease in peptic activity was achieved by the use of the low fat diet and large amounts of sodium alkyl sulfate. It is of interest that the higher values for peptic activity were obtained invariably with the specimens of gastric content aspirated during the evening. As shown in the table, the size of the ulcer was not reduced significantly by detergent therapy. The patient's clinical course was characterized by severe ulcer pain, often awakening him at night. This distress which had been previously controlled by the use of calcium carbonate, atropine and gastric aspirations, was totally unrelieved by the administration of sodium alkyl sulfate. The patient subsequently underwent a subtotal gastric resection from which he recovered uneventfully. Gross and microscopic study revealed a large benign ulcer of approximately the same measurements as determined by the initial gastroscopic and roentgen examinations. Despite the ingestion of 177.4 gms. of sodium alkyl sulfate in 28 days, there were no toxic symptoms. The blood, urine, serum bilirubin and renal function (urea clearance test) remained normal.

Case 2. N. O. (Unit No. 301052) a 41 year old male had had ulcer symptoms for four years. Roentgen examination revealed a large ulcer crater on the posterior wall of the midportion of the stomach, "probably benign but malignancy not ruled out."

At gastroscopy an oval, 8 mm. long and 4 mm. wide benign-appearing ulcer was seen on the posterior wall of the stomach at depth II. Treatment comprised the use of calcium carbonate, atropine, nightly gastric aspirations and a course of roentgen irradiation (13) directed to the fundus of the stomach. The ulcer decreased in size temporarily, but several weeks later a definite increase was noted in the size of the crater; a second, 4 mm. long benign ulcer was discovered in the same region of the stomach. Ulcer symptoms persisted and treatment was changed to the use of a low fat diet and sodium alkyl sulfate. It was recognized that no evaluation of the action of sodium alkyl sulfate on the healing of gastric ulcer could be made in this case inasmuch as the roentgen irradiation had gradually produced a histamine-achlorhydria.

TABLE 1

Peptic activity and pH of gastric contents, gastroscopic and x-ray observations in case 1

THERAPY	DAY OF TREATMENT	PEPTIC ACTIVITY RANGE	pH RANGE	GASTROSCOPY	X-RAY
		milliunits			
Low fat diet	Control	917–1345	1.78–3.5	Enormous benign ulcer, anterior wall lesser curvature just above angulus; length 2–3 cm., width 1.5 cm. and depth 1 cm. Mucosa normal	Huge ulcer crater, lesser curvature of stomach. Same dimensions as noted under gastroscopy
	Control	868–1133	1.64–2.2		
Low fat diet plus sodium alkyl sulfate 0.6 gm. hourly, twelve times daily for 17 days. Then 0.5 gm. hourly, ten times daily for 11 days	3	581–772	1.55–1.88		
	5	473–848	1.65–2.22		
	8			No significant decrease in size of ulcer; adjacent mucosa edematous	
Total intake of sodium alkyl sulfate = 177.4 gms. in 28 days	9				Ulcer possibly slightly smaller
	11	351–708	1.55–5.38		
	15	234–822	1.50–3.28	Ulcer possibly smaller; adjacent mucosa nodular	Crater smaller but still remains large; "presumably but not certainly a benign ulcer"
	24			No change; ulcer remains huge	
5 days after conclusion of detergent therapy				No change in size of ulcer	Crater has decreased in size by 5 mm.

The ulcer subsequently disappeared completely, a result probably attributable to the elimination of free HCl from the gastric content as a result of the X-Ray Therapy. The experiment, therefore, was continued only to study the possible toxic effects of the detergent. 7.2 to 7.8 gms. of sodium alkyl sulfate were given in divided hourly doses for the first 23 days and 6.5 gms. daily for the last 10 days of the experimental period, a total intake of 243 gms. in 33 days. Despite the enormous amount of detergent taken by the patient he complained only of a decrease in appetite which was temporary and a moderately severe diarrhea which was easily controlled by the use of tincture of opium. Repeated blood counts and urine analyses were normal. The serum bilirubin, cholesterol and cholesterol esters and the intravenous hippuric acid test likewise remained normal.

Case 3. A. K. (Unit No. 148136) a 68 year old woman had been treated for many years at the University Clinics for a benign gastric ulcer. This and the next case were considered especially suitable for the present study inasmuch as the lesion had proved so resistant to antacid therapy. In addition to numerous roentgen examinations of the stomach, the patient had undergone 65 gastroscopies, which had demonstrated a benign ulcer high on the lesser curvature, located on an elevation produced by a large hour-glass fold. The lesion on several occasions had disappeared but invariably recurred despite the continued use of alkalies.[2]

TABLE 2

Peptic activity and pH of gastric contents and gastroscopic observations in case 3

THERAPY	DAY OF TREATMENT	PEPTIC ACTIVITY RANGE	pH RANGE	GASTROSCOPY
		milli-units		
Low fat diet	Control	581–702	1.83–2.70	Elliptical, punched out ulcer high on lesser curvature, upon an elevation produced by a large hour-glass fold—adjacent mucosa edematous and hemorrhagic
	Control	430–772	1.7 –2.90	
Low fat diet plus sodium alkyl sulfate, from 5.0 to 8.4 gms. (usually 6.9 gms.) daily in divided hourly doses for 38 days	4	0–330	1.80–6.88	
	15			No change in size of ulcer; approximately 6–8 mm. long and 2–3 mm. wide
	28			No change; mucosa swollen and bled easily
Total intake = 258 gms.	36			Ulcer smaller, possibly 2–4 mm. long and 1 mm. wide; mucosa normal
3 weeks after conclusion of detergent therapy				No change in size of ulcer; increased redness and edema of surrounding mucosa .

The experimental data are recorded in table 2. Despite a definite lowering of peptic activity, no significant change in the size of the ulcer was observed gastroscopically. The intake of 258 gms. of sodium alkyl sulfate in 38 days is the largest administered thus far to a human subject. The patient complained of nausea and a decrease in appetite (attributable in part, at least, to the unpalatable diet) and also of a mild diarrhea. Frequent complete blood counts, urine analyses and measurements of the serum bilirubin, cholesterol, cholesterol esters, and intravenous hippuric acid test remained normal.

[2] This Case and Case 4 have been reported in detail by Palmer, Schindler and Templeton.[14]

Case 4. W. G. (Unit No. 144032) a 53 year old male had experienced ulcer symptoms intermittently for 22 years. He had been observed at the University Clinics for approximately seven years. During this time 37 roentgen examinations of the stomach and 82 gastroscopies had been performed, most of which had demonstrated a round, moderately deep, benign ulcer on the anterior wall of the lesser curvature just above the angulus. Although the lesion varied in size and disappeared completely at times, it invariably recurred despite persistent treatment both at home and in the hospital. In table 3 are recorded the quantity of sodium alkyl sulfate given, the peptic activity and pH of the gastric content and the course of the ulcer as demon-

TABLE 3

Peptic activity and pH of gastric contents and gastroscopic observations in case 4

THERAPY	DAY OF TREATMENT	PEPTIC ACTIVITY RANGE	pH RANGE	GASTROSCOPY
		milli-units		
Low fat diet	Control	128–538	1.90–6.62	Round, moderately deep 5 mm. long ulcer just above angulus; adjacent mucosa reddened and edematous
	Control	149–665	1.85–4.24	
Low fat diet plus sodium alkyl sulfate 0.5 gm. hourly ten times daily for 4 days	3	167–473	2.0 –6.20	
	6	106–234	2.1 –6.58	
Sodium alkyl sulfate 1.0 gm. hourly, ten times daily for 21 days	9			Ulcer possibly 3 mm. long; otherwise, no change
	10	85–473	3.6 –6.98	
Total intake of sodium alkyl sulfate 230 gms. in 25 days	13	64–494	3.45–7.02	
	17	85–494	2.4 –7.1	
	18			Ulcer possibly less deep; otherwise, no change
	20	41–430	3.75–6.6	
	24	106–408	4.4 –6.76	
	25			No change in ulcer; mild superficial gastritis
44 days after conclusion of sodium alkyl sulfate therapy...				Slight increase in length and width of ulcer

strated by gastroscopy. It is obvious that no significant change occurred in the peptic activity or in the size of the ulcer crater despite the ingestion of 230 gms. of sodium alkyl sulfate in 25 days. The only untoward symptom reported by the patient was a mild diarrhea which subsided in two days. Frequent analyses of the blood, urine, serum bilirubin, cholesterol, cholesterol esters and the intravenous hippuric acid test were normal.

COMMENT

The present study demonstrates that lipids can interfere with the inhibitory effect of sodium alkyl sulfate on peptic activity in man as well as in vitro.

No explanation can be offered for the mechanism of this action. The data show further that, in contrast to in vitro and dog experiments, it is difficult to lower peptic activity in man by means of sodium alkyl sulfate and the use of a low fat diet. As pointed out previously (11), the inhibition of peptic activity which is accomplished is usually a temporary one.

Contrary to the clinical observations of Fogelson and Shoch, sodium alkyl sulfate exerted no apparent beneficial effect on the course of gastric ulcer in the patients studied. Case 1, in particular, demonstrates that a definite lowering of peptic activity without change in the pH of the gastric contents does not relieve ulcer pain. Inasmuch as peptic activity was not eliminated completely, the possibility remains that its total inhibition might be associated with more favorable clinical results.

The absence of significant demonstrable toxic effects in these patients despite the ingestion of huge quantities of sodium alkyl sulfate is of great interest. The only reference to the toxicity of sodium alkyl sulfate which has come to our attention is the study by Hatton, Fosdick and Calandra (15). These workers administered from 30 to 60 mg. of Irium (mostly sodium lauryl sulfate with a small percentage of other sulphated alcohols of varying molecular weight) daily to active albino rats for as long as 8 weeks. All the animals survived the experiment and gained weight. No gross changes were noted in any of the organs, especially the liver, kidney, stomach or intestine. Microscopic examination revealed degenerative changes in the liver and intestinal mucosa. The authors point out that the amounts of Irium used were very greatly in excess of that found in toothpastes and powders. Although no clinical evidence of hepatic, gastric, or intestinal injury was noted in these studies, it should be emphasized that, until more information is obtained regarding their toxicity, detergents should be administered to man only under carefully controlled conditions.

CONCLUSIONS

1. Sodium alkyl sulfate given hourly in large doses in conjunction with milk and cream does not produce a detectable decrease in the peptic activity of the gastric contents in man.

2. Sodium alkyl sulfate given hourly in large doses in conjunction with a diet low in fat may decrease appreciably, though temporarily, the peptic activity of the gastric contents in man.

3. The healing of gastric ulcer is not affected by the use of very large quantities of sodium alkyl sulfate and a low fat diet.

4. Enormous quantities of sodium alkyl sulfate may be administered to man without apparent toxic effects.

BIBLIOGRAPHY

1. Shoch, D., and Fogelson, S. J.: Proc. Soc. Exp. Biol. & Med., **50**: 304, 1942.
2. Shoch, D., and Fogelson, S. J.: J. Ind. & Eng. Chem., **33**: 17, 1941.
3. Shoch, D., and Fogelson, S. J.: Quart. Bull. Northwest. U. Med. Sch., **16**: 142, 1943.
4. Walpole, S. H., Varco, R. L., Cook, C. F., and Wangensteen, O. H.: Proc. Soc. Exp. Biol. & Med., **44**: 619, 1940.
5. Varco, R. L., Code, C. F., Walpole, S. H., and Wangensteen, O. H.: Am. J. Physiol., **33**: 475, 1941.
6. Fogelson, S. J., and Shoch, D.: Physiology Seminar. Univ. of Chicago, 1943.
7. Beazell, J. M., Schmidt, C. L., Ivy, A. C., and Monogham, J. F.: Am. J. Dig. Dis., **5**: 661, 1938.
8. Bucher, G. R., and Beazell, J. M.: Am. J. Physiol., **133**: 213, 1941.
9. Anson, M. L., and Mirsky, A. E.: J. Gen. Physiol., **16**: 59, 1932.
10. Warren, I. A., Front, J., and Kirsner, J. B.: Gastroenterology, **1**: 102, 1943.
11. Kirsner, J. B., and Wolff, R. A.: Proc. Soc. Exp. Biol. & Med., **54**: 11, 1943.
12. Quick, A. J.: Am. J. Dig. Dis., **6**: 716, 1939.
13. Palmer, W. L., and Templeton, F. E.: J. A. M. A., **112**: 1429, April 15, 1939.
14. Palmer, W. L., Schindler, R., and Templeton, F. E.: Am. J. Dig. Dis., **5**: 501, 1938.
15. Hatton, E. H., Fosdick, L. S., and Calandra, J.: J. Dental Research, **19**: 87, 1940.

THE LARGE INTESTINE: A REVIEW OF CURRENT LITERATURE

E. E. WOLLAEGER, M.D., AND J. A. BARGEN, M.D.
Division of Medicine, Mayo Clinic, Rochester, Minnesota

POLYPS

There seems to be very little question in the minds of authors who deal with the subject of adenomatous polyps of the colon, that these tumors are definitely related to the development of carcinoma. Jackman (76) presented a case in which two polyps of the rectosigmoid were found by proctoscopic examination, but the patient refused to accept proper treatment for them. Five years later an annular carcinoma was found at the same site. Smedal (134) reported that of 827 cases of malignancy of the colon and rectum, in 14 per cent the growths were true malignant adenomas arising from polyps. According to him, reported clinical examinations indicate that about 70 per cent of polyps of the colon are in that portion of the bowel which is visible through the sigmoidoscope. Approximately the same percentage of colonic malignant tumors is situated in this segment. However, at necropsy a smaller percentage of polyps than this is found in the rectum and lower part of the sigmoid. This probably means that a fairly large number of polyps in the upper part of the colon are not diagnosed at clinical examination.

Phillips (111) pointed out the necessity of considering all polyps to be malignant and treating them so. Their occurrence in infants and children was discussed by Kennedy (80). Rankin (117) discussed the surgical treatment of diffuse or congenital adenomatosis in which the polyps are situated along the entire mucous lining of the colon. For this disease, the entire colon frequently must be extirpated and an ileac stoma established. Sometimes it is possible to perform subtotal colectomy and ileosigmoidostomy, with fulguration of rectal polyps.

Felsen (51) pointed out again the distinction between (1) adenomatosis (diffuse polyposis) of the colon and (2) polyposis cystica intestini associated with chronic ulcerative colitis. The latter is an inflammatory lesion and consists essentially of small islands of intact mucosa separated by linear and geographical ulceration. It does not predispose to malignancy.

The importance of recognizing and properly treating polyps cannot be overemphasized, since their eradication is the only means known by which the development of colonic carcinoma can be prevented.

CARCINOMA

Pathogenesis.—Bargen, Cromar and Dixon (13) advanced evidence that carcinoma of the colon arises from a precancerous inflammatory condition.

The fact that new cancerous growths occur in segments of bowel that remain after apparent complete surgical extirpation of a cancer of the colon, suggests that a potentially malignant region has been left behind. In studying apparently uninvolved colonic tissue removed at the time of resection of a carcinoma, the investigators found small adenomas in one third of their cases. In this same tissue they frequently found evidence of disordered repair of epithelium, associated with an underlying inflammatory process. The authors postulated that a primary inflammatory reaction in the submucous layers damages the epithelium of the colon and that subsequent repair may take place in a disorderly manner, leading to formation of adenomas and eventually, possibly, to the growth of carcinoma. The frequency of occurrence of multiple primary malignant lesions of the large bowel is further evidence for the idea that there is some defect in the normal mechanism for control of growth in the colons of some patients [Schweiger and Bargen (131); Rankin and Johnston (119)].

Pathology.—Some interesting data were presented by Coller, Kay and MacIntyre (29) concerning the regional lymphatic metastasis of carcinoma of the colon (excluding the rectum). By special methods directed at the finding of lymph nodes, they showed that such metastasis is of much more common occurrence than the ordinary methods of dissection would indicate. Some involvement of regional lymph nodes was found in 60.87 per cent of forty-six cases of carcinoma of the colon; the percentage was slightly higher in the presence of right colonic lesions than it was in the presence of left colonic lesions. The findings of the investigators indicated that the size of a lymph node is not a reliable index of the presence or absence of carcinomatous metastasis and that failure to find enlarged nodes at the time of surgical operation does not mean that metastasis has not occurred. Gilchrist (59) gave figures similar to those of Coller, Kay and MacIntyre for the incidence of metastasis to lymph nodes in cases of malignancy of the large bowel. To the surgeon, these papers are of great interest since they emphasize the importance of wide resection in all cases of colonic cancer if the disease is to be eradicated. Mechling (101) found that lymphatic metastasis from carcinoma of the rectum occurs in the direction of the flow of lymph and becomes retrograde only when blockage of lymphatic channels occurs.

The papers of Oosting (104) and of Laird (85), by means of reports of cases, give some idea of the incidence of cancer of the large bowel among children less than fifteen years of age.

Diagnosis.—The importance of early diagnosis of cancer of the large bowel was stressed by many writers [Hartzell (66), Imes (75), Palmer (106), Chamberlin (27), Cohn (28), Case (24), Gershon-Cohen and Shay (57), Alberts (5), Voldeng (144), Waldron (145), Graham (60), Heyd (70), Ludwick (91) and Rose (123)].

Complications.—Estes (41) considered the common and serious complication of cancer of the large bowel, namely, perforation. It is usually a late sign of the disease and occurs in about 10 per cent of cases. The perforation may take place through the growth itself or proximal to the tumor (usually in the cecum) as a result of obstruction. The attempt should be made to avoid perforation by early diagnosis and treatment of carcinoma, and by proper management of obstruction. The commonly occurring complication of colonic malignancy, obstruction, not infrequently occurs even in the presence of a surgically resectable lesion. Gregg and Dixon (63) stated that primary resection should not be performed in these circumstances and that often preliminary decompression by cecostomy or colostomy will be necessary. In their series of 121 cases they found that the ultimate prognosis was not as good when obstruction was present.

Urological complications following surgical operation for carcinoma of the rectum are of very frequent occurrence, according to Seaman and Binnig (133), who expressed the belief that many such complications are secondary to interference with the nerve supply to the bladder. The authors recommended rather complete preoperative and postoperative urologic study of patients with carcinoma of the rectum. Ewert (42) reported that in about 29 per cent of cases, complications develop in the urinary tract after surgical operation anywhere on the large bowel. Such complications are of more common occurrence among men than among women, and are more likely to appear after operations involving the rectal segment than those involving other portions of the large intestine. When prostatic obstruction was present, transurethral resection was sometimes necessary and was best done following the operation on the colon rather than preliminary to it.

Treatment.—A great many papers were devoted to some phase or other of surgical treatment of carcinoma of the colon. As would be expected, there is great divergence of opinion in regard to technics used by different surgeons. From reading over these contributions, the impression is obtained that each patient who has this disease must be individualized and the proper surgical treatment chosen according to the particular requirements of the patient and the preferences and abilities of the surgeon. No single procedure is applicable in all instances, even if the tumor involves the same segment of bowel. Statistical summaries of surgical experience concerning resectability of colonic carcinomas, operative mortality and postoperative survival time are difficult to compare one with another. However, the individual reports are interesting and many of them are most encouraging in that they indicate that more people who have this disease are receiving the benefits of surgical treatment, at lower risk and with better end results, than was formerly the case.

Rankin (116) discussed the general principles involved in surgical treatment

for colonic cancer and stressed the importance of proper preoperative and postoperative care. He found the resectability of tumors to be about 75 per cent, and operative mortality to be between 5 and 10 per cent. Hunt (73), in considering surgical treatment of carcinoma of the intraperitoneal portion of the colon, stressed the importance of early diagnosis and of individualization of treatment in obtaining good surgical results. The problem of operability is difficult and the usual criteria of inoperability, such as size of growth, fixation, and enlargement of regional lymph nodes, are not always reliable. Usually the matter of resectability can be decided only at the time of surgical operation, unless obvious contraindications to surgical measures are present.

Gregg and Dixon (64), in reviewing the records of 9,632 patients seen between the years 1907 and 1938, on whom the diagnosis of carcinoma of the colon or rectum had been made, were able to present some interesting statistics. Of their entire group of patients, about 75 per cent were subjected to surgical operation and 50 per cent underwent resection in an attempt at cure. The hospital mortality was 17 per cent (by patients) among all patients operated on. The authors found the five year survival rate to vary inversely with the degree of malignancy of the tumor (as graded by Broders).

Bargen, Cromar and Dixon (12) made an interesting study of so-called "early carcinoma" of the large bowel. They (31) included in their series (sixty-one cases) only growths less than 2.5 cm. in diameter and excluded all polypoid lesions. Actually they found that most of these tumors were not early, since all but two of them had given symptoms, such as bleeding or obstruction, which are really complications and therefore late signs of the disease. In nine cases there was involvement of regional lymph nodes and, in four, metastasis to the liver. The five year survival rate following radical surgical procedures in this group was 46 per cent, about the same as that obtained for all operable colonic cancers, irrespective of size. Here again the authors demonstrated that size of a lesion was of relatively little prognostic importance as compared to grade of malignancy (Broders) and age of patient.

Hayes and Burr (68) summarized their experiences in treatment of forty patients with cancer of the sigmoid, rectum and anus. Heard (69), Brooks and Ashley (23) and Bieren (19) discussed surgery of the large bowel in general, with special reference to treatment of carcinoma. Wangensteen (147) recommended aseptic methods in resection of the gastro-intestinal tract and described his technic. Although the surgeon himself is still the most important factor in operative mortality following resection of portions of the gastro-intestinal tract, meticulous care in regard to preoperative and postoperative treatment is of great importance, particularly proper administration of fluids. The author considered these measures in detail. Primary anastomosis was also rec-

ommended and discussed by Metheny (102) and Gibbon and Hodge (58). Koster (81) presented a method of resection and primary anastomosis in which the danger of peritonitis is minimized by exteriorization of the portion of bowel which is the site of the anastomosis, and later replacement of it in the peritoneal cavity. Operation in multiple stages was advocated by Fallis (43) and by De Courcy (32). Scannell (127) and Rosser (124) expressed the belief that, as yet, graded operations and exteriorization procedures cannot be entirely abandoned. In treating patients for malignant lesions of the lower portion of the sigmoid and rectum, Mayo (95), on the other hand, has found one-stage, combined, abdominoperineal resection to be increasingly applicable, although he declared that no single operation is suitable for all patients. The operative mortality in a series of 179 cases in which one-stage, combined, abdominoperineal resection was pérformed was 8.5 per cent. Continued experience with this method has given progressively better results since the author was able to report no deaths among the last seventy-five patients subjected to operation. Dunphy (38) recommended anterior resection for certain malignant lesions of the rectosigmoid of which the location is such that combined abdominoperineal resection is not necessary to remove all the node bearing tissue. Lamson (86), and Bergeret and Livory (18) described other operations for lesions of the rectosigmoid by which the anal sphincter could be maintained in use.

McKittrick (99) discussed the diagnosis and surgical treatment of carcinoma of the right portion of the colon. A summary of the clinical findings and the results of treatment in a large group of cases of carcinoma of the cecum, ascending colon and hepatic flexure was presented by Mayo and Lovelace (96). They studied the records of 885 patients who were seen between the years 1907 and 1938 and found that malignant lesions of this segment comprised about 12 per cent of the carcinomas of the entire large bowel. Surgical resection, with a view to cure of the disease, was attempted in 67 per cent of the cases in the entire group. Of those subjected to one-stage resection, the operative mortality (by patients) was 22.2 per cent and for two-stage procedures it was 28.9 per cent. Aside from this advantage in mortality, the one-stage procedure meant a shorter stay in the hospital, it removed the malignant tumor at an earlier time and resulted in a slightly better five year survival record than did multiple stage procedures. This does not mean that one-stage procedures should be attempted on all patients with cancers of the right portion of the colon. But when such procedures are possible and surgically advisable, they have definite advantages. Lenormant (88) advocated a one-stage resection with anastomosis for dealing with carcinomas of the transverse colon.

In considering advanced carcinoma of the colon and rectum, Phillips and Dixon (112) made the point that surgical exploration is often very much worth-while. Seemingly inoperable lesions not infrequently have been resected

with favorable results and, when this has not been possible, palliative operations often have brought much comfort to the patient. In certain instances, large, fixed lesions have been brought within the limits of operability by the use of radium or roentgen rays. Gregg and Dixon (62) presented cases illustrative of the advisability of surgical exploration for patients with what appear to be recurrent malignant growths of the colon. These seemingly recurrent growths may turn out to be: 1) benign lesions; 2) new, primary tumors which merit as radical removal as did the first malignant process; 3) local recurring tumors, removal of which may be followed by years of comfortable living or even permanent relief.

The use of the Miller-Abbott tube to facilitate surgical operations involving resection of the colon was discussed by Hartzell (67), who recommended its use preoperatively in all cases of colonic obstruction. He warned, however, of the need for caution since the method is not always successful in relief of distention of the large bowel. He agreed with McKittrick and Warren (100) that intestinal suction is especially helpful in facilitating one-stage resection of the right side of the colon by relieving tension on suture lines.

After reading the articles dealing with treatment of carcinomas of the large bowel by means of radium and roentgen rays, one is left with the impression that surgical operation is the treatment of choice and that radiation therapy may be used in conjunction with it or as a palliative measure. Doub, Pratt and Jones (34) expressed the belief that irradiation is of value, either alone or together with surgical measures, in all cases in which carcinoma involves the distal segment of the bowel. In early cases, according to them, irradiation may be curative. It may enhance the effect of operation and may render resectable lesions that originally seem inoperable. In inoperable cases palliation frequently can be achieved. The authors recommended a preoperative course of treatment with roentgen rays in all cases in which surgical intervention is employed. Bowing and Fricke (22) discussed the indications for, and the technic of, radium treatment for cancer of the rectum and rectosigmoid. Roberts (122) expressed himself in favor of treatment with roentgen rays for inoperable cancer of the rectum. For the most part, he opposed colostomy as a palliative measure for this condition since, he said, this procedure neither prolongs life, relieves distress or makes patients more comfortable. For this reason, roentgen rays rather than radium is the treatment of choice since proper application of radium ordinarily requires colostomy.

MISCELLANEOUS TUMORS OF THE COLON

Carcinoid tumors arising in the colon were discussed in several articles [Mayo and Wilson (97); Waugh and Snyder (148); Ashworth and Wallace (8)] in spite of the apparent rarity of their occurrence in this location.

Reports of individual cases of lipoma of the colon, reticulum cell sarcoma

of the cecum, and hemangioma of the large bowel were presented by Gault and Kaplan (56), by Greaves (61) and by Hunt (74).

Patton and Patton (108), and Blaikley (20) each reported a case in which endometriosis involved the sigmoid colon and caused intestinal obstruction. The former two authors reviewed the symptoms of colonic endometriosis and pointed out that the lesion rarely involved the mucosa of this organ and therefore did not often cause bleeding by rectum. Intestinal obstruction is not a common complication. Surgical exploration usually is necessary although castration by irradiation has been recommended.

COLOSTOMY

Good general reviews on the indications and proper use of colostomy and other defunctioning procedures as adjuncts to intestinal surgical measures were given by Duncan (37), and also by Jennings (77). Both stressed the point that the type of procedure carried out must depend on the individual situation. Colostomy is an integral part of many surgical operations directed at cure of serious colonic disease and, as such, it must be looked on as a lifesaving measure. An unjustified attitude of pessimism toward colostomy on the part of the physician, and also the patient, not infrequently has resulted in withholding of curative treatment. Specific types of colostomy, and particular problems encountered in the management of them, were discussed in several contributions [Hogeboom (71), Allen and Welch (6), Steinberg (138), Archer and Riley (7), Stone (139), and Judd (78)]. Mathewson's (94) article on preliminary colostomy in the management of gastrocolic and gastrojejunocolic fistulas is thought-provoking. When the fecal stream is diverted by this procedure, the diarrhea from which these patients suffer stops almost at once and general improvement takes place. The author expressed the belief that the diarrhea is caused by regurgitation of fecal material into the small bowel rather than by the short-circuiting which the fistula produces. Evidence of this is found in cases of gastrocolic fistula, in which condition diarrhea ordinarily does not occur unless the fistula is very large. Whatever the reason for cessation of the diarrhea following establishment of a colonic stoma, from a practical standpoint such a stoma would seem to be of great value, and it may help to lower the high mortality rate which is still associated with surgical repair of gastrocolic and gastrojejunocolic fistulas.

MEGACOLON

There is still no universally satisfactory treatment for this condition, judging from the variety of treatments recommended. Soper (135) expressed the belief that operations on the sympathetic nervous system are of no avail and he recommended complete resection of the involved colon. In mild

cases, medical measures suffice. Kredel and Beach (83) and also Leriche (89) seemed enthusiastic about sympathectomy. The latter presented favorable reports of cases. Leriche also mentioned a series of cases in which colectomy was done for this disease with unsatisfactory results. In his opinion, colectomy is a dangerous operation and should be done only when changes in the bowel are very marked and no response is obtained from sympathectomy. Barenberg, Greene and Greenspan (11) reported a case in which satisfactory clinical results were obtained by the use of acetyl-beta-methylcholine bromide after all other methods (including partial sympathectomy) had failed.

"CHRONIC ULCERATIVE COLITIS"

The designation used in the foregoing heading is still used to indicate all types of ulcerative colitis. This may be in part responsible for the variety of views concerning etiology.

Etiology.—Dragstedt, Dack and Kirsner (35) summarized the evidence implicating Bacterium necrophorum as a causative agent in this disease. The fact that anerobic organisms continue to grow in the diseased colon following ileostomy, while aerobic organisms disappear, suggests that the anaerobes are responsible for the continued infection in these defunctionalized colons. The authors have been able to isolate the anaerobic Bacterium necrophorum in a majority of cases of the disease and also have demonstrated specific antibodies in the blood of patients suffering from chronic ulcerative colitis. They presented evidence of the pathogenicity of this organism for man in a variety of pathologic processes.

Weiss, Slanger and Goodfriend (150) expressed the belief that any of a variety of organisms isolated from the nasopharynx of a patient with chronic ulcerative colitis may be causally related to the colonic disease, especially when the same organism can be isolated simultaneously from the rectosigmoid. They reported encouraging therapeutic results in fifteen cases of ulcerative colitis by injecting vaccines made from these organisms.

A study of the incidence of fungi in the stools of patients with chronic ulcerative colitis was reported by Swartz and Jankelson (141). By cultural methods they found some fungi to be present in 80 per cent of the stools from patients who had colitis and in only 33 per cent of the stools from normal people used as controls. The authors made no claim as to the etiologic significance of these findings but felt that further studies along this line were justified.

Felsen (50) classified cases of colitis in two main groups: those in which the infecting agent attacks the bowel directly and those in which infections outside the enteric structures are primary and bring about their secondary effect on the bowel by means of toxins, viruses, emboli and so forth. He included

chronic ulcerative colitis in the first group and reviewed again the evidence which led him to feel that this disease is a chronic form of bacillary dysentery.

The work of Poppe (114), in reproducing ulcerative colitis in dogs, is of interest. The lymphatic drainage of the ileocecal segment was obstructed and acute enteritis, with ulceration of the colon, resulted. Although the the pathologic changes brought about were similar to those of ulcerative colitis, and in some ways to regional enteritis in man, no definite conclusions could be drawn regarding the role of lymphatic obstruction in the causation of these diseases. Sandler (126) recommended that patients with chronic ulcerative colitis and so-called mucous colitis be given a diet low in carbohydrates. On the basis of not entirely convincing evidence, he expressed the belief that the tissues of patients with these diseases do not utilize glucose normally, and he reported cases to demonstrate clinical improvement of patients on a low carbohydrate intake.

Diagnosis.—The differential diagnosis of various inflammatory and functional diseases of the colon was discussed by Palmer (107). Paulson (109) reviewed the value of, and proper indications for, various diagnostic procedures in studying ulcerative disease of the large bowel.

Treatment.—Rankin and Johnston (118) considered the various forms of ulcerative colitis to be primarily medical diseases and expressed the belief that in about 15 per cent of cases complications develop which require surgical operation. Many of the acute complications, such as hemorrhage, perforation, acute fulminating colitis and perianal and perirectal infections are best treated conservatively. The more chronic complications, such as the development of polyps or malignant disease, sometimes require surgical measures. Surgical operation also is indicated for the badly damaged bowel which has no remaining capacity for physiologic function. The problem of when to operate is difficult to solve and often a long period of rehabilitation, with medical treatment, is necessary before operation is feasible.

The most obvious trend in the literature regarding treatment of these difficult diseases is a tendency to emphasize surgical measures. Several articles are devoted primarily to this subject and experienced surgeons are advocating that surgical treatment be offered to more patients and that it be undertaken earlier in the course of the disease. Garlock (55) summarized his experiences with surgical treatment in twenty-five cases and gave his indications for surgical measures. Cave (25) and Cave and Thompson (26) presented a similar report and emphasized the importance of prolonged medical investigation and treatment before resort is had to surgical operation. They expressed the belief, however, that the primary factor tending toward mortality in their series was the fact that surgical intervention frequently is offered too late in the course of the disease, when the patient is so depleted that he is unable to

withstand a major procedure. Lahey (84) took a similar stand. Kahn and Bay (79) expressed the belief that about 25 per cent of patients with various forms of "chronic ulcerative colitis" will require surgical treatment.

The clinical study of Elsom and Ferguson (40) is of great interest in evaluating the relative merits of medical and surgical therapy. They conducted a follow-up study of a group of twenty-three patients treated medically and another group of twenty-seven patients who received both medical and surgical treatment. These patients all had severe chronic ulcerative colitis and were encountered over a period of twelve years. The mortality in the two groups was approximately the same. The results of treatment were more favorable in the surgical group since most of these patients were able to return to their previous occupations and to lead relatively normal lives, in spite of the fact that they had external fistulas.

An article by Mackie (93) on ulcerative colitis represents the accumulation of many years of experience with this disease and, in the article, the author summarized a concept of etiology, pathogenesis and treatment based on this experience. Mackie (93) pictured a disease in which a number of factors may have primary or secondary etiologic significance. His therapeutic approach, therefore, also was directed from many angles. In his experience, surgical treatment became necessary in about a fourth of the cases.

Detailed descriptions of measures available in the medical treatment of the disease were given by Reed and Rochex (121) and also by Kraemer (82). Schwyzer (132) reported his experiences with surgical treatment. Therapy with concentrated liver extract and with vitamin B_1 in twelve cases of chronic ulcerative colitis was reported by Schiffer and Ferguson (128). They concluded that these substances have no specific effect against this disease. The use of neoprontosil was recommended by Stanford and McMillan (137). Schwartzman and Grossman (130) reported a case in which the administration of sulfaguanidine resulted in no benefit and toxic symptoms developed. Using this same drug on rats, however, Bloomfield and Lew (21) were able to demonstrate that it had a definite prophylactic effect against the spontaneous cecitis that develops in these animals.

Various complications of chronic ulcerative colitis were illustrated by reports of cases. Welch and Gorham (151) performed ileostomy, and later colectomy, on a patient with catatonic schizophrenia. The mental symptoms cleared after this surgical treatment. Necrotizing skin lesions associated with chronic colitis were related to nutritive deficiency by Felsen (52). Lindahl and Bargen (90) reported several cases of nephrolithiasis following ileostomy for ulcerative colitis, and expressed the belief that the basis for the development of nephrolithiasis may be the infection in the colon which is not eradicated by ileostomy.

In a disease so notoriously difficult to treat satisfactorily, attempts at new forms of therapy are certainly justified and to be encouraged. However, the results of any form of treatment are difficult to evaluate and it is important to maintain a conservative and skeptical attitude toward them until their value has been proved.

AMEBIASIS

The production of amebiasis in experimental animals has thrown light on a number of problems connected with infestation with Endamoeba histolytica in man. Faust (47) summarized pertinent experimental findings and related them to the human problem. In connection with the so-called carrier state, it is of interest that no evidence was found for "lumen parasitism." In other words, there was always evidence of destruction of tissue if an animal harbored this parasite. Neither was there any evidence that secondary infection with bacteria is necessary for invasion or destruction of tissue. Increase in virulence of Endamoeba histolytica by repeated passage through dogs has been demonstrated. In considering the various laboratory diagnostic measures for amebiasis, Faust (47) concluded that microscopic examination of stools is still the most practical and most reliable one.

Howell and Knoll (72) discussed the incidence of amebiasis among infants and children and gave evidence that this incidence is probably on the increase.

OTHER INFLAMMATORY DISEASES OF THE COLON

The roentgenologic diagnosis of tuberculosis of the intestine was discussed by Hare (65), who pointed out that the differential diagnosis cannot always be completely made by this method. The finding of a pulmonary tuberculous infection is of great help.

Barber and Murphy (10) reviewed etiologic considerations, pathology, symptomology and diagnosis of lymphogranuloma venereum. They considered particularly the surgical treatment in cases in which conservative treatment has been of no avail. Palliative surgical procedures for relief of fistulas and strictures usually are of only temporary benefit. Often colostomy, either with or without resection of the involved rectal segment, becomes necessary.

The present status of chemotherapy for infestation with various intestinal parasites was ably reviewed by Faust (48). A symposium on food-borne diseases of the gastro-intestinal tract, including epidemiology, diagnosis, prevention and treatment, reveals again the tremendous importance of proper inspection of food and proper sanitary measures to keep under control these ever threatening diseases [Bercovitz (17), McKim (98), Perkins (110)].

Ravenal and Smith wrote a favorable report on the treatment, with sulfapyridine and sulfathiazole, of bacillary dysentery of children. Further con-

trolled studies along the same lines certainly are indicated. Felsen (49) described a syndrome which he called "acute focal nonspecific enterocolitis." This is an inflammatory condition of the bowel secondary to some systemic disease outside the enteric tract. He expressed the belief that the bowel is vulnerable to such inflammations because it serves as one important organ for elimination of toxins from the body.

A rare but nevertheless important disease to consider when dealing with acute conditions of the abdomen is so-called simple ulcer of the cecum, colon and rectum. Barlow (14) was able to find in the literature reports of seventy-eight such cases and added two more to the list. These ulcers can occur in any segment of the colon but are of most common occurrence in the cecum; symptomatically they often simulate acute appendicits. The only practical treatment is surgical operation, since the lesions have a great tendency to cause perforation and peritonitis.

The results of experimental and clinical studies of sulfanilylguanidine as an intestinal antiseptic were reported by Firor and Poth (54). They demonstrated that the number of coliform bacteria in the stools can be markedly reduced if the drug is administered in adequate doses. Because of limited absorption from the bowel and rapid excretion, the concentration of the drug in the blood is usually not very high. Symptoms of toxemia may occur but are not severe. Use of the same drug in preoperative preparation of patients for surgical operation on the colon was reported by Firor and Jonas (53) who expressed the belief that the risk of postoperative peritoneal infection was reduced by employment of the agent. Apparently, the bacteriostatic effect of succinylsulfathiazole on the coliform bacteria of the bowel is similar to that of sulfanilylguanidine, according to results obtained by Poth and Knotts (115), who administered the drug to dogs.

Weinstein and Rammelkamp (149) tested the bactericidal influence of gramicidin, when given by mouth, on the gram-positive Lactobacillus acidophilus in the gastro-intestinal tracts of mice. Although gramicidin has been shown to have a bactericidal effect on gram-positive organisms in vitro and in vivo, no effect could be demonstrated from extremely large doses on the growth of the organism named under the conditions of the experiment.

In considering the diagnosis of disorders of the bowel in general, Bercovitz (16) made a special study of cellular exudates of intestinal discharges. He concluded that the presence of white or red blood cells always signifies pathologic changes in the wall of the bowel and that organic disease of the bowel can be ruled out by negative findings after painstaking search of the stools for cells. Schulte (129) discussed in great detail the differential diagnosis between inflammatory tumors and true neoplasms of the colon. Roentgenologic methods are of great assistance.

PHYSIOLOGY

Oppenheimer (105) has made a detailed study of the position of the colon in normal subjects by means of roentgenologic methods employed after a barium meal. Many so-called congenital anomalies of the colon were found to correspond to physiologic variations in position due to motor activity of the bowel. Of interest was his finding that the position of the cecum, ascending colon, transverse colon and sigmoid may vary with changes in tone of the bowel. The cecum never was situated in the true pelvis, although the appendix sometimes was. Contrary to a widely held belief, stasis in the cecum and ascending colon is physiologic.

A series of studies on the motility of the colons of both human beings and experimental animals was carried out by Ivy and his co-workers (2, 3, 4). They used balloons, either singly or in tandems, introduced into the human colon through a colonic stoma. Motility was measured by recording on smoked drums the pressure changes in the balloons. They found that adjacent segments of the colon for the most part do not simultaneously manifest integrated motility. A wave of activity in any one segment of colon would cause propulsion of intestinal content only if the distal segment of the colon accepted the wave and contracted similarly. The frequent failure of the distal segment to do this, they wrote, might cause cramp-like sensations and might be the explanation for the symptoms attributed to an irritable colon. In studying the effect of alcohol on colonic motility in both dogs and man it was found that propulsive activity was stimulated. Morphine was found to stimulate activity of the colon but this effect could be antagonized in part by injection of atropine. Beazell and Ivy (15) measured the amount of flatus passed by apparently normal individuals and obtained a mean value of 527 cc. per day.

IRRITABLE COLON

Good reviews of present ideas concerning the causative factors, diagnosis and proper treatment of the irritable colon were presented by Collins and Van Ordstrand (30) and also by Rumsey (125). The basis for the report by the first two authors was an analysis of the records of 1000 consecutive cases in which this diagnosis was made. Because the clinical picture associated with irritable colon can simulate almost any other abdominal disease, the importance of making a proper diagnosis is obvious; in the absence of proper diagnosis, patients not uncommonly are subjected to fruitless surgical procedures. The diagnosis can be made only by exclusion of all local, systemic and reflex causes of colonic dysfunction, so that complete laboratory studies usually are necessary. The excessive use of cathartics or irritating enemas was considered a contributing factor in 45 per cent of the cases.

Fantus, Wozasek and Steigman (45) attempted, by microscopic and chemical

study of stools, to provide methods for differential diagnosis between functional and organic disease of the colon. The intermittent presence of excessive amounts of mucus in the stools, especially in strings or formations of membranous nature, may be a sign of "irritable colon." If constantly present, these findings indicate a lesion of the colon, although the authors do not indicate what type of lesion is meant. White blood cells and excessive protein in the stools signify the existence of inflammatory or ulcerative colonic disease. Using the finding of excessive mucus as a sign of irritability of the colon, the authors were unable to demonstrate any irritating effect from the ingestion of bran (46).

Drueck (36) discussed dietary treatment of the irritable colon. Diathermy as a therapeutic measure was recommended by Zeiter and Renshaw (152).

ALLERGY OF THE GASTRO-INTESTINAL TRACT

Thomas and Wofford (143) reviewed their findings and the results of treatment of 134 patients who had received the diagnosis of gastro-intestinal allergy. The various foods found to be responsible for symptoms were identified largely by means of food diaries and use of elimination diets; skin tests for these foods were positive in only 40 per cent of cases. Of the entire group of patients, 90 per cent had allergic symptoms referable to organs other than the gastro-intestinal tract. The response to treatment, consisting of removal of offending foods from the patient's diet, could not be well evaluated because of incomplete follow-up information. However, many patients previously on a regimen for irritable colon did not progress well until offending foods were eliminated.

As an aid to the discovery of specific sensitiveness affecting patients suspected of having allergic gastrointestinal symptoms, Thomas and Renshaw (142) advocated a method by which the reaction of the rectal mucosa to various allergens is observed through the proctoscope. The allergen to be tested is applied directly to a localized area of mucosa, which is subsequently observed for evidence of erythema, edema or engorgement. No very good data were given as to the accuracy of this method and, with the obvious technical difficulties involved, its field of usefulness must be limited.

VITAMINS

The prevalence of vitamin deficiency among patients with lesions of the colon was again emphasized by Mackie (92), who stressed the importance of discovering such deficiency and correcting it before any surgical treatment was attempted. He expressed the belief that, by this means, operability can be improved and operative mortality reduced. If lack of any one vitamin is demonstrated, a multiple deficiency must be assumed and therapy administered on this basis. Drueck (36) pointed out that vitamins of the B complex are

19. Bieren, R. E.: Surg., Gynec. & Obst., 72: 611, 1941.
20. Blaikley, J. B.: Proc. Roy. Soc. Med., 34: 810, 1941.
21. Bloomfield, A. L., and Lew, W.: Proc. Soc. Exper. Biol. & Med., 48: 363, 1941.
22. Bowing, H. H., and Fricke, R. E.: Radiology, 37: 569, 1941.
23. Brooks, C. D., and Ashley, L. B.: J. Michigan M. Soc., 40: 43, 1941.
24. Case, J. T.: Illinois M. J., 80: 145, 1941.
25. Cave, H.: Proc. Inter-State Post-Grad. M. A. North America (1940), p. 378, 1941.
26. Cave, H. W., and Thompson, J. E.: Ann. Surg., 114: 46, 1941.
27. Chamberlin, D. T.: S. Clin. North America, 21: 837, 1941.
28. Cohn, Isidore: South. Surgeon, 10: 173, 1941.
29. Coller, F. A., Kay, E. B., and MacIntyre, R. S.: Ann. Surg., 114: 56, 1941.
30. Collins, E. N., and Van Ordstrand, H. S.: Cleveland Clin. Quart., 8: 67, 1941.
31. Cromar, C. D. L., Bargen, J. A., and Dixon, C. F.: Proc. Staff Meet., Mayo Clin., 16: 641, 1941.
32. DeCourcy, J. L.: M. Times, New York, 69: 151, 1941.
33. Dixon, C. F.: Proc. Inter-State Post-Grad. M. A. North America (1940), p. 250, 1941.
34. Doub, H. P., Pratt, J. P., and Jones, H. C.: Radiology, 37: 575, 1941.
35. Dragstedt, L. R., Dack, G. M., and Kirsner, J. B.: Ann. Surg., 114: 653, 1941.
36. Drueck, C. J.: M. Rec., 152: 435, 1940.
37. Duncan, J. A.: Northwest Med., 40: 120, 1941.
38. Dunphy, J. E.: Arch. Surg., 43: 1076, 1941.
39. Eggers, C.: Ann. Surg., 113: 15, 1941.
40. Elsom, K. A., and Ferguson, L. K.: Am. J. M. Sc., 202: 59, 1941.
41. Estes, W. L.: Pennsylvania M. J., 44: 1407, 1941.
42. Ewert, E. E.: J. Urol., 46: 764, 1941.
43. Fallis, L. S.: Texas State J. Med., 37: 463, 1941.
44. Fansler, W. A.: Tr. Am. Proct. Soc., 41: 231, 1940.
45. Fantus, B., Wozasek, O., and Steigmann, F.: Am. J. Digest. Dis., 8: 296, 1941.
46. Fantus, B., Wozasek, O., and Steigmann, F.: Am. J. Digest. Dis., 8: 298, 1941.
47. Faust, E. C.: Rev. Gastroenterol., 8: 197, 1941.
48. Faust, E. C.: J. A. M. A., 117: 1331, 1941.
49. Felsen, Joseph: Mississippi Valley M. J., 63: 20, 1941.
50. Felsen, Joseph: Rev. Gastroenterol., 8: 8, 1941.
51. Felsen, Joseph: Am. J. Roentgenol., 45: 551, 1941.
52. Felsen, Joseph: New York State J. Med., 41: 2228, 1941.
53. Firor, W. M., and Jonas, A. F.: Ann. Surg., 114: 19, 1941.
54. Firor, W. M., and Poth, E. J.: Ann. Surg., 114: 663, 1941.
55. Garlock, J. H.: Ann. Surg., 113: 2, 1941.
56. Gault, J. T., and Kaplan, P.: Am. J. Surg., 53: 145, 1941.
57. Gershon-Cohen, J., and Shay, Harry: Pennsylvania M. J., 44: 462, 1941.
58. Gibbon, J. H., Jr., and Hodge, C. C.: Ann. Surg., 114: 635, 1941.
59. Gilchrist, R. K.: Illinois M. J., 80: 249, 1941.
60. Graham, A. S.: South, M. J., 34: 812, 1941.
61. Greaves, F. C.: U. S. Nav. M. Bull., 39: 558, 1941.
62. Gregg, R. O., and Dixon, C. F.: Proc. Staff Meet., Mayo Clin., 16: 177, 1941.
63. Gregg, R. O., and Dixon, C. F.: S. Clin. North America, 21: 1143, 1941.
64. Gregg, R. O., and Dixon, C. F.: Proc. Staff Meet., Mayo Clin., 16: 657, 1941.
65. Hare, H. F.: S. Clin. North America, 21: 829, 1941.
66. Hartzell, J. B.: J. Michigan M. Soc., 40: 36, 1941.
67. Hartzell, J. B.: J. Michigan M. Soc., 40: 277, 1941.
68. Hayes, H. T., and Burr, H. B.: South M. J., 34: 806, 1941.
69. Heard, J. E.: Tri-State M. J., 14: 2568; 2576, 1941.
70. Heyd, C. G.: Proc. Inter-State Post-Grad. M. A. North America (1940), p. 282, 1941.

71. Hogeboom, G. W.: J. Missouri M. A., 38: 20, 1941.
72. Howell, K. M., and Knoll, E. W.: Am. J. Dis. Child., 61: 54, 1941.
73. Hunt, V. C.: California & West. Med., 53: 258, 1940.
74. Hunt, V. C.: Surgery, 10: 651, 1941.
75. Imes, P. R.: South. M. J., 34: 538, 1941.
76. Jackman, R. J.: Proc. Staff Meet., Mayo Clin., 16: 11, 1941.
77. Jennings, W. K.: S. Clin. North America, 21: 259, 1941.
78. Judd, E. S.: Proc. Staff Meet., Mayo Clin., 16: 117, 1941.
79. Kahn, Maurice, and Bay, M. W.: Tr. West. S. A. (1940), 50: 493, 1941.
80. Kennedy, R. L. J.: Am. J. Dis. Child., 62: 481, 1941.
81. Koster, Harry: Am. J. Surg., 53: 248, 1941.
82. Kraemer, Manfred: Rev. Gastroenterol., 8: 357, 1941.
83. Kredel, F. E., and Beach, M. W.: J. South Carolina M. A., 37: 11, 1941.
84. Lahey, F. H.: New York State J. Med., 41: 475, 1941.
85. Laird, T. K.: Am. J. Surg., 53: 335, 1941.
86. Lamson, O. F.: Northwest Med., 40: 117, 1941.
87. Laufman, Harold: Internat. Abstr. Surg., 73: 222, 1941; Surg., Gynec. & Obst. (Sept.) 1941.
88. Lenormant, Charles: Presse méd., 49: 281, 1941.
89. Leriche, René: Presse méd., 49: 89, 1941.
90. Lindahl, W. W., and Bargen, J. A.: J. Urol., 46: 183, 1941.
91. Ludwick, N. V.: Rev. Gastroenterol., 8: 388, 1941.
92. Mackie, T. T.: Tr. Am. Proct. Soc., 41: 245, 1940.
93. Mackie, T. T.: Tr. & Stud., Coll. Physicians, Philadelphia, 9: 1, 1941.
94. Mathewson, C., Jr.: Ann. Surg., 114: 1004, 1941.
95. Mayo, C. W.: S. Clin. North America, 21: 1129, 1941.
96. Mayo, C. W., and Lovelace, W. R., Jr.: Tr. West. S. A. (1939), 49: 378, 1940; (Abstr.) Surg., Gynec. & Obst., 72: 698, 1941.
97. Mayo, C. W., and Wilson, W. D.: Minnesota Med., 24: 178, 1941.
98. McKim, O. E.: New York State J. Med., 41: 1433, 1941.
99. McKittrick, L. S.: Rhode Island M. J., 24: 161, 1941.
100. McKittrick, L. S., and Warren, R.: J. A. M. A., 117: 345, 1941.
101. Mechling, C. C.: Tr. Am. Proct. Soc., 41: 223, 1940.
102. Metheny, David: Northwest Med., 40: 239, 1941.
103. Morgan, J. W.: J. A. M. A., 117: 1335, 1941.
104. Oosting, Melvin: Ohio State M. J., 37: 1067, 1941.
105. Oppenheimer, Albert: Am. J. Roentgenol., 45: 177, 1941.
106. Palmer, Douglass: Tr. Am. Proct. Soc., 41: 182, 1940.
107. Palmer, W. L.: Mississippi Valley M. J., 63: 158, 1941.
108. Patton, C. L., and Patton, R. J.: Am. J. Surg., 53: 265, 1941.
109. Paulson, Moses: Am. J. Clin. Path., 11: 588, 1941.
110. Perkins, J. E.: New York State J. Med., 41: 1438, 1941.
111. Phillips, R. B.: Mil. Surgeon, 88: 258, 1941.
112. Phillips, R. B., and Dixon, C. F.: Proc. Staff Meet., Mayo Clin., 16: 182, 1941.
113. Poate, H. R. G.: Australian & New Zealand J. Surg., 11: 110, 1941.
114. Poppe, J. K.: Arch. Surg., 43: 551, 1941.
115. Poth, E. J., and Knotts, F. L.: Proc. Soc. Exper. Biol. & Med., 48: 129, 1941.
116. Rankin, F. W.: Surg., Gynec. & Obst., 72: 332, 1941.
117. Rankin, F. W.: South. Surgeon, 10: 615, 1941.
118. Rankin, F. W., and Johnston, C. C.: South. M. J., 34: 464, 1941.
119. Rankin, F. W., and Johnston, C. C.: Internat. Clin., 2: 246, 1941.
120. Ravenal, S. F., and Smith, D. L.: South. M. J., 34: 504, 1941.
121. Reed, A. C., and Rochex, Francis: Northwest Med., 40: 332, 1941.

122. ROBERTS, F.: Brit. M. J., **1**: 357, 1941.
123. ROSE, T. F.: M. J. Australia, **2**: 501, 1941.
124. ROSSER, CURTICE: South. Surgeon, **10**: 874, 1941.
125. RUMSEY, J. M.: J. Missouri M. A., **38**: 152, 1941.
126. SANDLER, B. P.: Rev. Gastroenterol., **8**: 157, 1941.
127. SCANNELL, J. M.: M. Times, New York, **69**: 333, 1941.
128. SCHIFFER, PAUL, AND FERGUSON, L. K.: Am. J. Digest. Dis., **8**: 300, 1941.
129. SCHULTE, A.: Arch. f. klin. Chir., **199**: 465, 1940.
130. SCHWARTZMAN, JOSEPH, AND GROSSMAN, LEO: Arch. Pediat., **58**: 734, 1941.
131. SCHWEIGER, L. R., AND BARGEN, J. A.: Arch. Int. Med., **66**: 1331, 1940.
132. SCHWYZER, ARNOLD: Minnesota Med., **24**: 54, 1941.
133. SEAMAN, J. A., AND BINNIG, C.: J. Urol., **46**: 777, 1941.
134. SMEDAL, M. I.: S. Clin. North America, **21**: 845, 1941.
135. SOPER, H. W.: Am. J. Roentgenol., **46**: 655, 1941.
136. STALKER, L. K., RULISON, E. T., JR., AND WHITE, J. D.: Am. J. Digest. Dis., **8**: 440, 1941.
137. STANFORD, W. R., AND MCMILLAN, LOUISE: North Carolina M. J., **2**: 131, 1941.
138. STEINBERG, M. E.: Am. J. Surg., **53**: 463, 1941.
139. STONE, M. M.: Am. J. Surg., **53**: 374, 1941.
140. STRYKER, W. A.: Arch. Path., **31**: 670, 1941.
141. SWARTZ, J. H., AND JANKELSON, I. R.: Am. J. Digest. Dis., **8**: 211, 1941.
142. THOMAS, J. W., AND RENSHAW, R. J. F.: Cleveland Clin. Quart., **8**: 17, 1941; South. M. J. **34**: 528, 1941.
143. THOMAS, J. W., AND WOFFORD, C. P.: Am. J. Digest. Dis., **8**: 311, 1941.
144. VOLDENG, K. E.: J. Kansas M. Soc., **42**: 97, 1941.
145. WALDRON, G. W.: Texas State J. Med., **37**: 13, 1941.
146. WALKLING, A. A.: Pennsylvania M. J., **44**: 1318, 1941.
147. WANGENSTEEN, O. H.: Surg., Gynec. & Obst., **72**: 257, 1941.
148. WAUGH, J. M., AND SNYDER, J. M.: Proc. Staff Meet., Mayo Clin., **16**: 689, 1941.
149. WEINSTEIN, LOUIS, AND RAMMELKAMP, C. H.: Proc. Soc. Exper. Biol. & Med., **48**: 147, 1941.
150. WEISS, SAMUEL (New York), SLANGER, ALEXANDER, AND GOODFRIEND, SANFORD: J. Lab. & Clin. Med., **26**: 1925, 1941.
151. WELCH, C. S., AND GORHAM, L. W.: Am. J. Surg., **52**: 511, 1941.
152. ZEITER, W. Z., AND RENSHAW, R. F.: Arch. Phys. Therapy, **22**: 453, 1941.

SOME OBSERVATIONS ON SPECIFIC VITAMINS AND ATROPHIC GASTRITIS[1]

NATHAN SHAPIRO, M.D.,[2] LEON SCHIFF, M.D., HENRY S. BLOCH, ELLEN S. GARBER, M.S., AND MARY J. HANNAHER, B.S.

From the Department of Internal Medicine, College of Medicine, University of Cincinnati, and the Gastric Research Laboratory of the Cincinnati General Hospital, Cincinnati, Ohio

INTRODUCTION

In 1935 Jones, Benedict, and Hampton (1) suggested that atrophy of the gastric mucosa, which was long thought to represent an end stage of a chronic inflammatory process (Faber (2)), might be due to a deficiency state. They observed the disappearance of gastroscopic changes of atrophic gastritis in patients with pernicious anemia following adequate liver therapy, an observation which has since been confirmed by others (3). The rapid change from an atrophic to a normal mucous membrane was considered to represent "... an epithelial change associated with successful treatment of a specific deficiency state rather than the healing of a chronic inflammatory process" (1).

Following liver therapy, improvement in the gastroscopic appearance of atrophic gastritis not associated with pernicious anemia has been reported by many observers (4). Schiff and Goodman (5) reported the disappearance of atrophic changes following the oral administration of large doses of desiccated hog's stomach (Ventriculin). Olleros (6) demonstrated improvement of the atrophic gastritis present in sprue following the use of liver extract. Schindler, Kirsner, and Palmer (7) reported restoration of the gastric mucosa to normal following liver extract therapy in 4 of 8 cases of atrophic gastritis. Abels (8) observed disappearance of atrophic changes in the gastric mucosa in 3 of 8 patients following large doses of brewer's yeast. Adding weight to the possible role of deficiency factors in gastritis are the observations that atrophic gastritis is almost constantly seen in pernicious anemia and occurs very commonly in pellagra, sprue, and in vitamin deficiency states in general (9).

Because of these facts we have studied a group of patients with atrophic gastritis for evidences of deficiency disease and for signs of benefit following the administration of specific vitamins.

METHOD OF STUDY

Thirteen clinic and hospital patients with "uncomplicated" atrophic gastritis[3] were investigated for evidences of nutritional disease. They were carefully examined for clinical stigmata of deficiency; their dietary histories were

[1] This work was aided by a grant from the National Cancer Institute.

[2] Fellow of the National Cancer Institute, 1940-1943.

[3] Atrophic gastritis not associated with any other recognizable disease of the stomach or with pernicious anemia.

analyzed for possible inadequacies, and their blood and urine were assayed for vitamin A and carotene and thiamin respectively. Ten control subjects of similar economic status with miscellaneous conditions but without gastroscopic evidence of atrophic gastritis were similarly studied. Clinic patients were admitted to the hospital for a five-day period during which time a complete medical and dietary history was obtained, and physical, neurological, roentgenological, and gastroscopic examinations were made. Laboratory studies, including complete blood counts and gastric analyses, were also carried out. In evaluating the dietary history, which was obtained by one of us, M. J. H., a trained dietitian, the criteria employed were based largely on the "recommended allowances" of the Council on Food and Nutrition (10) except for the caloric allowances which we considered to be too liberal. The maintenance of the individual's weight was used as an added guide in determining adequacy of caloric intake. The patients fell into two groups: those with adequate and those with deficient diets. We allowed 0.6 mg. of thiamin per thousand calories as recommended by the Council as representing adequate thiamin nutrition. We then followed the vitamin requirement formula of 1:1.5:10 for thiamin to riboflavin to niacin as advocated by Bing (11) which gives values corresponding to those of the Council.

After determining the various food-stuffs ingested by the patients, a typical menu was set up covering a two-day period. The average daily vitamin content of thiamin, riboflavin, niacin, and vitamin A was calculated from food value tables.[4] When indicated, the methods of food preparation were taken into consideration in calculating vitamin intake.

Determination of urinary thiamin, thiamin tolerance, and plasma vitamin A and carotene. Immediately after admission the patients were placed on a weighed diet consisting of approximately 1800 calories with 200 grams of carbohydrate, 75 grams of protein, and 60 grams of fat. The thiamin, niacin, riboflavin, and vitamin A content was calculated as follows:

Thiamin[5]	.824	mg.
Niacin	33	mg.
Riboflavin	2.0	mg.
Vitamin A (and Carotene)	9000	I.U.

After the subjects had been on the diet one day, collection of twenty-four hour urine specimens was started. Immediately after lunch (the largest meal) of the following day, the patient was given 5 mg. of thiamin chloride by mouth and collection of the second twenty-four hour urine specimen was started (12). The urinary thiamin determinations were performed according to the method of Melnick and Field (13).[6]

[4] Compiled by Sarah Merritt Wenger, Director of Education, Wisconsin Alumni Research Foundation.

[5] From table of R. R. Williams and T. D. Spies (Vitamin B_1 (Thiamin) and Its Use in Medicine, New York, The Macmillan Company, 1938, p. 112).

[6] Ellen S. Garber was instructed in this method at the University of Michigan through the courtesy of Dr. Henry Field.

The normal values, according to Melnick and Field, are a twenty-four hour urinary excretion of 90 micrograms of thiamin for males and 60 micrograms for females, and the excretion of 7 per cent or more of a 5 mg. test dose in subjects on an adequate diet (12). Later, for convenience, the Melnick and Field procedure was replaced by the thiochrome method of Ferrebee and Carden (14). The conditions for the oxidation of thiamin to thiochrome were modified according to Conner and Straub (15). The fluorescence was measured with the Lumetron photoelectric colorimeter (Model 402 EF) set up as a fluorometer.

The vitamin A and carotene determinations were done on fasting samples of blood plasma taken on three different days and the average values computed. Determinations of vitamin A and carotene were first carried out by the method of Clausen and McCoord (16). Later, analyses were done by the photocolorimetric method of Kimble (17)[7] which was slightly modified for the Lumetron colorimeter (Model 402 EF). The normal values of Clausen and McCoord for vitamin A and carotene are vitamin A = 10–30 "Blue" units per cent and carotinoid pigments = 77–110 "Carotinoid" units per cent. Using the photocolorimetric method of Kimble, we found normal values[8] for males to vary from 96 I.U.% to 191 I.U.% with an average of 137 I.U.%, and 0.096 mg.% to 0.288 mg.% with an average of 0.149 mg.% for vitamin A and carotene respectively. For females the values were slightly lower varying from 82 I.U.% to 139 I.U.% with an average value of 107 I.U.%, and 0.053 mg.% to 0.300 mg.% with an average value of 0.165 mg.% for vitamin A and carotene respectively.

RESULTS OF STUDIES

Table I shows the clinical evidences of nutritional deficiency in 13 patients with atrophic gastritis. Patients J. T. and J. F. had typical magenta color tongues, while patient N. M. had a moderately reddened tongue. In patient J. T. diffuse atrophy of the papillae was present, while in J. F. only the papillae along the edge were atrophic. Cheilosis was likewise present in patients J. T. and J. F. None of these subjects had objective evidence of peripheral neuritis; patient N. M. who was a lactating mother with sprue, complained of parasthesias which subsided immediately after admission. Five of the patients had anemia, two normocytic, two microcytic, and one macrocytic. Small intestinal changes compatible with deficiency states were present in 3 of 6 patients whose small bowels were studied. None of the subjects had any other recognizable clinical manifestations of deficiency disease.

Upper abdominal complaints varying in duration from a few months to many years were predominant in almost all the patients. Episodes of diffuse epigastric pain or "soreness" unrelated to meals were not infrequent. Fullness soon

[7] We wish to thank Dr. Jules C. Abels and Alice T. Gorham of the Memorial Hospital, New York, for giving us the benefit of their experience with this method.

[8] Forty-seven vitamin A and carotene determinations were done on members of the resident hospital staff, nursing staff, and technicians, consisting of 10 males and 8 females who ate an average normal diet containing about 5000 units of vitamin A per day. Care was taken to exclude anyone who might have had supplementary carotene or vitamin A for at least two months prior to analysis.

after eating was quite common. Excessive belching and passing of flatus also predominated. Constipation was the rule; diarrhea was present in patient N. M. only. Nausea was infrequent. Slight weight loss was common. Seven subjects had a posthistamine achlorhydria. Very few of the patients had significant coexisting diseases. Patient E. C. had an associated irritable colon; W. O., cholelithiasis which was probably asymptomatic; J. T. and W. K., moderately severe hypertrophic arthritis and generalized arteriosclerosis, while W. K. also had mild hypertension. Patient J. F. had a mild psychoneurosis, while E. J. had a gastrointestinal neurosis. Patient J. P. had a rectal stricture due to lymphopathia venereum.

TABLE I

Clinical evidences of nutritional deficiency in 13 patients with "uncomplicated" atrophic gastritis

NO.	PATIENT	AGE	SEX	ANEMIA	GLOSSITIS	CHEILOSIS	PERIPHERAL NEURITIS	X-RAY CHANGES IN SMALL INTESTINE
1	E. C.	55	f	0	0	0	0	0
2	J. T.	73	m	Microcytic	+	+	0	+
3	W. O.	66	m	0	0	0	0	−
4	W. K.	65	m	0	0	0	0	0
5	F. W.	59	m	0	0	0	0	−
6	W. G.	50	m	0	0	0	0	+
7	J. C.	69	m	Normocytic	0	0	0	−
8	M. S.	34	f	0	0	0	0	−
9	J. F.	58	f	0	+	+	0	+
10	J. P.	64	m	Normocytic	0	0	0	−
11	N. M.	33	f	Macrocytic	+	0	±	0
12	E. J.	43	m	0	0	0	0	−
13	M. G.	60	f	Microcytic	0	0	0	−

Table II lists the vitamin content of the diets of 12 patients with atrophic gastritis as determined by dietary history both before and after the onset of symptoms. The deficiencies were due to lack of meat and milk in the diet incurred largely by dislike for them. In some instances the diet was improved after the onset of gastric symptoms, because the patient resorted to increased use of such foods as milk and eggs. A change from white to whole wheat bread was also occasionally made. (Our nutritional studies were done prior to the use of enriched flour.) In other instances the diet was improved or restricted by the physician who saw the patient prior to study.

Obviously the atrophic gastritis does not necessarily condition the deficiency, at least as far as its symptomatology is concerned, for the dietary analyses indicate the presence of certain deficiencies prior to the onset of symptoms. That achlorhydria *per se* is not the conditioning factor is suggested by the fact that the number of patients with adequate intakes of riboflavin, niacin, and

vitamin A and carotene are equally distributed among the subjects both with and without free hydrochloric acid in their gastric contents. However, 4 of the 5 patients who had adequate intake of thiamin prior to onset of symptoms had achlorhydria.

Table III represents the urinary thiamin and blood vitamin A and carotene determinations compared with the intake of these vitamins in the period preceding the chemical studies. Of the 11 patients in whom attempt at correlation was possible, we found 10 in whom the twenty-four hour urinary thiamin excretion was in agreement with the dietary intake, especially if we consider the circumstances noted in the table under "Remarks." Following the tolerance test, however, 3 of the 11 patients failed to excrete the expected proportion of thiamin. The few discrepancies between thiamin intake and urinary excretion

TABLE II

Vitamin content of diets of 12 patients with "uncomplicated" atrophic gastritis*

	DIET DEFICIENT IN:			
	Thiamin	Riboflavin	Niacin	Vitamin A & Carotene
Prior to onset of symptoms				
Total deficient	7	5	4	3
Total adequate	5	7	8	9
After onset of symptoms				
Total deficient	7	7	3	3
Total adequate	5	5	9	9

* Patient No. 9 (J. F., Table I) omitted because of an unreliable history.

which were encountered were equally distributed between the patients with and without achlorhydria. Possible explanations for some of these discrepancies are included in the table.

There was good correlation between the intake of vitamin A and the plasma vitamin A levels (table III). In general the plasma carotene paralleled the vitamin A level.

Table IV represents the results of urinary thiamin and blood vitamin A and carotene determinations in a control group of 10 patients. In 6 of the 10 patients the twenty-four hour urinary thiamin excretion reflected the dietary intake accurately. There were only 2 patients with achlorhydria in this group, and the thiamin excretion irregularities did not occur in either of these.

In respect to vitamin A in the control subjects, 4 of the 10 showed plasma levels which did not check with the dietary intake. In No. 3 and 5, however, the discrepancy is explainable by the remarks noted.

TABLE III

Intake and quantitative estimation of vitamins in 13 patients with "uncomplicated" atrophic gastritis

NO.	PATIENT	SEX	FREE HCl	THIAMIN			VITAMIN A AND CAROTENE			REMARKS
				Intake	24-hour urinary excretion	Tolerance test	Intake	Vit. A blood level	Carotene blood level	
					micro-grams	*% excreted*				
1	E. C.	f	0	Adeq. years	191	9.4	Adeq. years	26.9 B.U.	91 C.U.	
2	J. T.	m	0	Def. years	68	2.4	Def. years	5.3 B.U.	59 C.U.	
3	W. O.	m	0	Adeq. years	101	2.9	Adeq. years	26.2 B.U.	150 C.U.	
4	W. K.	m	0	Adeq. years			Adeq. years	173 I.U.	0.105 mg.%	
5	F. W.	m	0	Def. 2 mos.	89	6.2	Def. 2 mos.	8.6 B.U.	107 C.U.	
6	W. G.	m	0	Def. years	36	20.8	Adeq. years	119 I.U.	0.164 mg.%	
7	J. C.	m	0	Adeq. 2 mos.	180	8.0	Adeq. 2 mos.	7.3 B.U.	67 C.U.	
8	M. S.	f	+	Def. 3 mos.	97	5.5	Adeq. years	94 I.U.	0.101 mg.%	
9	J. F.	f	+	?	112	7.7	?	86 I.U.	0.048 mg.%	History unreliable
10	J. P.	m	+	Def. 2 years	108	4.4	Adeq. years	23.4 B.U.	83 C.U.	1.1 mg. thiamin in test diet
11	N. M.	f	+	Def. 9 mos.	43	9.7	Def. 9 mos.	51 I.U.	0.013 mg.%	Lactating mother x 7 mos.
12	E. J.	m	+	Def. years	157	5.9	Adeq. years	24.1 B.U.	74 C.U.	Supplemental thiamin (1.0 mg.) irreg. x 9 mos.
13	M. G.	f	+	Adeq. years	92	7.1	Adeq. years	8.1 B.U.	44 C.U.	Vitamin content of diet borderline

Note: B.U. = blue units %; C.U. = carotinoid units %; I.U. = international units %.

TABLE IV

Intake and quantitative estimation of vitamins in control group of 10 patients

NO.	PATIENT	SEX	FREE HCl	DIAGNOSIS	THIAMIN			VITAMIN A AND CAROTENE			REMARKS
					Intake	24-hour urinary excretion	Tolerance test	Intake	Vit. A blood level	Carotene blood level	
						micrograms	*% excreted*				
1	E. D.	m	0	Chronic gall bladder disease	Adeq. years	175	7.2	Def. years	9.3 B.U.	32 C.U.	
2	R. H.	f	0	Gastric ulcer	Def. 6 mos.	43	2.6	Def. 6 mos.	20.1 B.U.	97 C.U.	
3	A. K.	m	+	Gastric ulcer	Def. 4 mos.	47	6.8	Def. 4 mos.	102 I.U.	0.080 mg.%	
4	L. L.	f	+	Duod. ulcer	Def. 5 mos.	27	1.2	Def. 5 mos.	64 I.U.	0.057 mg.%	Milk and cream 5 days before study
5	A. M.	m	+	Rectal ca.	Adeq. years	87	5.8	Adeq. years	4.1 B.U.	63 C.U.	Fever; liver metastases
6	N. T.	f	+	Ovarian ca.	Def. 6 mos.	85	3.5	Def. 6 mos.	13.6 B.U.	70 C.U.	Hosp. diet (1.2 mg. thiamin) x 6 days before study
7	A. T.	m	+	Bronchogenic ca.	Def. 8 mos.	154	4.6	Def. 8 mos.	4.6 B.U.	64.3 C.U.	Hosp. diet (1.2 mg. thiamin) x 6 days before study
8	J. G.	m	+	Gastric neurosis	Adeq. 3 wks.	122	5.6	Adeq. years	15.4 B.U.	77 C.U.	1.1 mg. thiamin in test diet
9	C. S.	m	+	Hemoptysis, probably bronchiectasis	Adeq. years	142	13.2	Adeq. years	19.8 B.U.	50 C.U.	
10	I. F.	f	+	Melena, ? etiology	Def. 3 yrs.	171	3.3	Adeq. years	19.2 B.U.	58 C.U.	1.1 mg. thiamin in test diet

Note: B.U. = blue units %; C.U. = carotinoid units %; I.U. = international units %.

The chemical results which depend on the vitamin intake preceding the determinations, confirm, in general, the dietary history. It is quite likely, therefore, that the dietary analyses prior to the onset of symptoms were reliable.

In our experience patients with achlorhydria do not necessarily excrete subnormal amounts of thiamin in the urine provided the diet has been adequate.

Results of specific vitamin therapy in patients with atrophic gastritis. After the conclusion of these studies, specific vitamin therapy was started on most of the patients with atrophic gastritis. Because of the inconvenience of coming to the laboratory so frequently and the dislike for gastroscopy, the group available for continued therapy dwindled to 5. These patients were very cooperative and therefore could be relied upon to appear as often as necessary for examination and treatment. All were free of fever and evidence of hepatic disease.

The subjects were nos. 1, 2, 3, 4, and 8 as listed in Table I. Patient E. C. had been followed in the Out-Patient Dispensary since February, 1938. From then until January, 1941, when she was started on specific vitamin therapy, she had been subjected to gastroscopy seven times, each examination revealing a diffuse atrophic gastritis.

Patient J. T. was admitted to the hospital because of symptoms of one and a half year's duration, suggesting gastrointestinal carcinoma. He also exhibited evidences of riboflavin and niacin deficiency. Gastroscopic examination showed diffuse atrophic gastritis of a severe degree following which therapy was started.

Patient W. O. had been admitted to the hospital because of a suspected gastric cancer. Over a period of eight months prior to treatment he was examined gastroscopically three times. The first examination showed superficial and erosive gastritis; the second, only superficial gastritis, and the third, superficial and moderately diffuse atrophic gastritis.

Patient W. K. had been followed in the Out-Patient Dispensary for three years because of digestive symptoms which had started fifteen years before. Two gastroscopic examinations before vitamin therapy was started, revealed a definite localized gastric atrophy.

Patient M. S. had been followed in the Out-Patient Dispensary for three years with the same symptoms which had been present intermittently for the previous seven years. She had been examined gastroscopically three times over a period of ten months. Each examination revealed a localized area of gastric atrophy.

Unfortunately, only 1 (J. T.) of the 5 patients who were treated with various vitamins had clinical evidences of nutritional deficiency.

Gastroscopic criteria of atrophic gastritis or gastric atrophy were the pres-

ence of branching vessels, either bluish or reddish in color, frequently associated with impromínence or absence of rugae and a grayish or greenish-gray discoloration of the mucosa.

Our plan of treatment was to give large doses of the vitamin orally each day and when available to inject a large dose parenterally three times a week for a period of two months. At the conclusion of each therapeutic period the patients were examined gastroscopically and changes in the mucosa noted. Only in patient J. T. was the diet changed significantly while under therapy because of a nutritional deficiency state. If it were thought that some improvement in the appearance of the mucosa had occurred, the same substance in a similar or larger dose was continued for another two months and the subject reexamined. Once a vitamin produced improvement, other vitamins were not administered. Our only criterion for improvement was complete, or

TABLE V

Vitamins and dosage used in treating 5 patients with atrophic gastritis

NO.	PATIENT	THIAMIN	RIBOFLAVIN	NIACIN AMIDE	PANTOTHENIC ACID	PARA-AMINO BENZOIC ACID	CHOLINE	VITAMIN A
1	E. C.	+	+	+	+	+	+	+
2	J. T.	+	+	+	+	+	+	+
3	W. O.	+	+	+	+	+	+	
4	W. K.	+	+		+		+	
8	M. S.						+	+
Dosage.....		10 mg. orally per day; 50 mg. parenterally 3 times per week	10 mg. orally per day; 5 mg. parenterally 3 times per week	300 mg. orally per day	50 mg. orally per day; 50 mg. parenterally 3 times per week	300 mg. orally per day	1.0–1.5 grams orally per day	100,000–200,000 U.S.P. units orally per day

almost complete, disappearance of the vessels characteristic of atrophic gastritis. Mere color changes or increased prominence of rugae were noted but were not considered significant since these variations are influenced by many factors (18). Repeated blood counts and gastric analyses following injection of histamine were done. No effect on the achlorhydria was noted. There were no apparent deleterious effects from the doses of vitamins employed.

Table V illustrates the vitamins and the dosage used in the different subjects. The specific vitamins were administered as follows: Thiamin chloride was taken daily as a 10 mg. tablet immediately after the largest meal and 50 mg. were injected either intravenously or intramuscularly three times per week on alternate days. Two and a half milligram tablets of riboflavin were taken after each meal and at bedtime. Five milligrams of crystalline riboflavin sodium were administered intravenously or intra-muscularly three times per week. Niacin amide was ingested in 100 mg. doses after each meal.

Pantothenic acid was administered orally as the calcium or sodium salt in amounts of 10 mg. five times per day. Fifty milligrams of a 5 per cent solution was injected parenterally three times per week. Para-aminobenzoic acid was taken in 100 mg. capsules after each meal, while choline chloride was taken in 250 mg. capsules after each meal and at bedtime, or two capsules after each meal, depending on dosage desired. Vitamin A in the form of plain Haliver Oil or vitamin A concentrate was administered as 100,000 U.S.P. units per daily dose in patients J. T. and M. S. and as 200,000 U.S.P. units per daily dose in patient E. C.

In none of our 5 subjects was there clinical evidence to suggest faulty absorption, nor did any have diarrhea. Thiamin determinations done in 2 and vitamin A determinations done in 3 patients during and after treatment with these vitamins indicated proper absorption. Meyer, Burton, and Sturgis (19) have shown that absorption of riboflavin and pantothenic acid is normal in patients with pernicious anemia, a condition in which both atrophic gastritis and achlorhydria are almost uniformly present.

All the patients were treated with choline, because improvement in the atrophic gastritis was noted gastroscopically in 2. In patient M. S. the vessels in a localized area of atrophy disappeared completely, and the color returned to normal following two months of choline (1.0 gm. daily). Patient W. O. showed remarkable improvement in the appearance of the gastric mucosa in that many of the previously visible vessels had disappeared after ten weeks of choline therapy. The latter was continued for several more months following which virtually all the vessels had disappeared and the mucosal color had returned to normal. The other 3 subjects showed no improvement following choline therapy. Patient E. C. was treated with 1.0 gram daily for four months and 1.5 grams daily for an additional month. Patient J. T. took the choline irregularly for two months without effect and hence was given 1.5 grams which he took regularly for two additional months without significant change. None of the other specific vitamins used in this study produced any significant gastroscopic changes.

The disappearance of the atrophic gastritis in M. S. and L. O. following choline therapy may have been spontaneous; but we believe that this is unlikely in view of the length of the control period of observation. However, further studies are necessary to settle this point. In this connection, the observation that choline is necessary to help maintain normal epithelium in the forestomach of rats may be of interest (20).

SUMMARY

1. A brief review of the literature suggests that atrophic gastritis may be due to a deficiency state, particularly of the vitamin B complex.

2. Clinical and dietary studies in a small group of patients with atrophic gastritis suggest that evidence of nutritional deficiency is somewhat more common in them than in a small control group.

3. Treatment of 5 patients having atrophic gastritis with large doses of thiamin, niacin amide, riboflavin, pantothenic acid, para-aminobenzoic acid, and vitamin A failed to produce any significant changes in the gastric mucosa as determined by gastroscopic examination.

4. Although 2 of the 5 patients showed disappearance of atrophic changes *gastroscopically* when treated with choline chloride, further observations are necessary to evaluate the effect of choline in this respect.

ACKNOWLEDGMENTS

We wish to thank Dr. Norman Weissman, formerly of the Biochemistry Department, College of Physicians and Surgeons, New York, for giving us the benefit of his experience with the thiochrome method of thiamin determination.

We also wish to thank Miss Dorothy McCrory, formerly of the Department of Dietetics, Cincinnati General Hospital, for her help with the nutritional histories.

The riboflavin injectable (Flavaxin Niphanoid), riboflavin oral (Flavaxin tablets), vitamin A concentrate, para-aminobenzoic acid, and calcium pantothenate tablets and 5 per cent solution (Pantothaxin) were furnished by Winthrop Chemical Company, Inc. through the courtesy of Mr. Vincent P. Carr of the Department of Medical Research.

The crystalline choline chloride was furnished by S.M.A. Corporation through the courtesy of Mr. R. A. Beeson.

The nicotinamide and choline chloride were furnished by Merck & Co., Inc. through the courtesy of Dr. D. F. Robertson.

The thiamin chloride (Crysto-Vibex), vitamin A (Haliver Oil Plain), and sodium d-pantothenate capsules were furnished by Parke, Davis & Company through the courtesy of Dr. E. A. Sharp.

REFERENCES

1. Jones, C. M., Benedict, E. B., and Hampton, A. O.: Am. J. M. Sc., 190: 596, 1935.
2. Faber, K.: Gastritis and Its Consequences. Copenhagen, Oxford University Press, 1935.
3. (a) Lehmann, R.: Les atrophies gastriques dans les anémies idiopathiques et les métanémies. Paris, E. Le François, 1936. (b) Chevallier, P., and Moutier, F.: Sang, 11: 935, 1937. (c) Schiff, L., and Goodman, S.: Ohio State M. J., 34: 1220, 1938. (d) Schindler, R., and Serby, A. M.: Arch. Int. Med., 63: 334, 1939.
4. Lehmann (3a), Chevallier and Moutier (3b), Schindler and Serby (3d), Aaron, A. H., and Murphy, H. M.: Lahey Birthday Vol., pp. 1–7, 1940.
5. Schiff, L., and Goodman, S.: Am. J. Digest. Dis., 7: 14, 1940.
6. Olleros, A. R.: J. Pub. Health & Trop. Med., 13: 503, 1938.
7. Schindler, R., Kirsner, J. B., and Palmer, W. L.: Arch. Int. Med., 65: 78, 1940.
8. Abels, J. C.: Personal communication.

9. (a) HENNING, N.: Die Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934. (b) GUTZEIT, K., AND TEITGE, H.: cited by SCHINDLER AND SERBY (3d). (c) SCHINDLER, R.: Gastroscopy: The Endoscopic Study of Gastric Pathology. Chicago, The University of Chicago Press, 1937. (d) OLLEROS (6). (e) RUFFIN, J. M., BROWN, I. W., JR., AND CLARK, E. H.: Am. J. Digest. Dis., **7:** 414, 1940. (f) SCHINDLER, KIRSNER, AND PALMER (7). (g) JONES, C. M.: Am. J. Digest. Dis., **8:** 205, 1941. (h) RUFFIN, J.: cited by JONES (9g). (i) BORLAND, J. L.: cited by JONES (9g). (j) KENAMORE, B.: Personal communication. (k) SCHIFF, L., GOODMAN, S., STEVENS, R. J., MOSS, H. K., AND SHAPIRO, N.: Unpublished observations.
10. The National Nutrition Conference, Pub. Health Rep., **56:** 1233, 1941.
11. BING, F. C.: M. Clin. North America, **27:** 287, 1943.
12. MELNICK, D., FIELD, H., JR., AND ROBINSON, W. D.: J. Nutrition, **18:** 593, 1939. ROBINSON, W. D., MELNICK, D., AND FIELD, H., JR.: J. Clin. Investigation, **19:** 399, 1940.
13. MELNICK, D., AND FIELD, H., JR.: J. Biol. Chem., **130:** 97, 1939.
14. FERREBEE, J. W., AND CARDEN, G. A.: J. Lab. & Clin. Med., **25:** 1320, 1940.
15. CONNER, R. T., AND STRAUB, G. J.: Indust. & Engin. Chem. (Analytical Ed.), **13:** 380, 1941.
16. CLAUSEN, S. W., AND MCCOORD, A. B.: J. Pediat., **13:** 635, 1938.
17. KIMBLE, M. S.: J. Lab. & Clin. Med., **24:** 1055, 1939.
18. RUFFIN, J. M., BROWN, I. W., JR., AND CLARK, E. H.: Am. J. Digest. Dis., **7:** 418, 1940. WOLF, S., AND WOLFF, H. G.: Am. J. Digest. Dis., **10:** 23, 1943.
19. MEYER, C. E., BURTON, I. F., AND STURGIS, C. C.: Proc. Soc. Exper. Biol. & Med., **49:** 363, 1942; Ibid, **50:** 251, 1942.
20. SHARPLESS, G. R., AND SABOL, M.: J. Nutrition, **25:** 113, 1943.

THE EFFECT OF A BLACKTONGUE-PRODUCING DIET UPON THE ENDOSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN THE DOG[1]

JOHN A. LAYNE, M.D., AND JAMES B. CAREY, M.D.
From the Department of Medicine, University of Minnesota, Minneapolis, Minnesota

INTRODUCTION

Since the appearance of the gastric mucosa has seldom been described in patients with pellagra, a study was designed to produce blacktongue in dogs, then to observe the changes in the gastric mucosa, if any, with relation to those of the mouth, and to note variations in the acidity of the gastric secretion with relation to the condition of the gastric mucosa. The importance of nicotinic acid deficiency in the pathogenesis of the decreased acidity of the gastric secretion is uncertain, since many patients with endemic pellagra have evidences of deficiency of other vitamins (12, 16, 19). The most striking signs and symptoms in experiemental blacktongue in the dog are inflammation of the oral and pharyngeal mucosa, anorexia, and diarrhea. The incidence of hypochlorhydria or achlorhydria is reported to be increased in pellagrins (6, 10, 14, 20).

METHOD OF EXPERIMENTATION

Five adult, female, mongrel dogs were used in this experiment. Blacktongue was produced a total of 9 times in the 5 dogs, by feeding them diet no. 123 of Goldberger and Wheeler (4). In 3 of the experiments, the animals received weekly injections of 10 mgm. of thiamin chloride in order to exclude any changes due to a deficiency of this substance in the diet. All of the animals had received the standard laboratory diet for two to three months before the start of the experiment and had been examined gastroscopically several times by the method previously described (7). Three determinations of acid gastric secretion (using 1.5 mgm. of histamine phosphate) were performed during the control period. After the start of the experiment, the dogs were examined gastroscopically at intervals of 7 to 14 days and the determinations of the acid gastric secretion were performed upon the fasting unanesthetized animals at intervals of 7 to 10 days. The determinations of gastric secretion were alternated with the gastroscopic examinations in such a way that the gastroscopic examinations were performed only several days after the last previous histamine test.

[1] Abridgment of a thesis submitted by Dr. Layne to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Medicine.

The dogs were maintained on the blacktongue-producing diet for periods of 74, 60, 69, 56, 102, 69, 56, 60 and 49 days, respectively. In all instances, marked inflammation of the oral and pharyngeal mucosa, anorexia, and diarrhea developed. In three instances the animals were sacrificed in order to obtain material for microscopic study of pathologic changes. In the remaining experiments, the disease was allowed to progress as far as was believed compatible with recovery before treatment was instituted. Therapy consisted of the intramuscular injection of nicotinic acid[2] and the resumption of the standard laboratory diet. In the dogs which were thus treated, the gastroscopic observations and the determinations of acid gastric secretion were continued until the animals had become normal.

OBSERVATIONS

A mild pallor of the gastric mucosa was observed in all but one of the experiments, after the animals had been maintained on the blacktongue-producing diet for 30 or more days. The development of anemia in dogs fed a blacktongue-producing diet has been reported previously (11, 17). In two of our experiments in which examination of the blood was performed at weekly intervals, the pallor of the gastric mucosa was accompanied by a fall in the erythrocyte count and hemoglobin percentage of the blood. In these two experiments pallor of the gastric mucosa was observed for the first time 39 and 41 days respectively after the blacktongue-producing diet had been started. At this time there had been a decrease of 16 and 30 per cent respectively in the erythrocyte count in the two animals, but only a fall of 8 per cent in the hemoglobin percentage (Sahli). The color of the mucosa usually was normal within four to six weeks after the animal resumed the standard laboratory diet.

A constant observation in these experiments was that the submucosal vessels of the stomach became more easily visible at the time of gastroscopy after the animals had been fed the blacktongue-producing diet for approximately five or more weeks. These changes occurred only in the upper half of the stomach, and were never observed in the antral or the pyloric regions, and in most instances occurred prior to the onset of inflammatory changes in the mouth. The sections of the stomach obtained from animals sacrificed at the height of a severe attack of blacktongue showed no atrophy of the mucosa. The ease with which the stomach of these animals was distended as well as the disappearance of the mucosal folds when the stomach was only mildly inflated, indicated that the increased visibility of the submucosal vessels was probably owing to a decreased tonus of the wall of the stomach. In most instances the decreased muscular tone of the gastric

[2] The nicotinic acid was supplied in a sterile solution combined with monoethanolamine ("Nicamin") through the courtesy of Abbott Laboratories, North Chicgao, Illinois.

wall was concomitant with loss of weight of the animals, and consequently may represent merely a decrease of general muscular tone. The appearance of the stomach in the animals which received additional thiamin did not differ in any significant respect from those which received the diet alone. In animals which were examined gastroscopically as early as six or seven days after the institution of treatment, the tonus of the stomach had returned to normal.

A mild hyperemia of the gastric mucosa was observed at one time or another in seven of the nine experiments. However, in all instances the reddening of the gastric mucosa subsided even though the inflammatory changes in the buccal mucosa became progressively more notable. The different response of the gastric mucosa to the disease may be associated with the fact that the stomach is an actively functioning secretory organ, and may be less susceptible to this particular deficiency. Moreover, the medium in which the cells are situated may condition their response to the nicotinic acid deficiency. The reaction of saliva as secreted is neutral or nearly so. The possibility exists that the acidity of the gastric secretion plays an appreciable role in preventing the entrance of microorganisms into the mucosa of the stomach and production of changes there which are similar to the changes in the mouth (15).

No other change was observed in the gastric mucosa of these animals. The small quantity of mucus occasionally present never exceeded the normal amount. Two small mucosal hemorrhages were seen on the anterior wall in the middle third of the stomach in one animal 43 days after the start of the Goldberger diet. When the stomach of this animal was examined gastroscopically 5 days later these mucosal erosions had disappeared and none reappeared subsequently. The absence of any characteristic changes in the gastric mucosa in these animals was confirmed by microscopic study of the sections of the stomach from the three animals which were sacrificed during a severe state of the disease.

No constant or significant change in acid gastric secretion occurred in any of the experiments, either during the period of production of the disease, at the height of the development of the oral lesions of blacktongue, or following treatment with nicotinic acid. The length of time which the animals received the nicotinic acid deficient diet had no demonstrable influence on gastric secretion. The results in the three experiments in which the animals received 10 mgm. of thiamin chloride intramuscularly each week to supplement any deficiency of this substance in the Goldberger diet, did not vary significantly from those in which the animals did not receive additional thiamin.

DISCUSSION

It would appear to be well established that the vitamin B complex is concerned with the integrity of the normal function of the gastrointestinal tract since disturbances due to a deficiency of this substance have been demonstrated

in many species of animals (1, 2, 5, 8). The only recorded observations of the appearance of the gastric mucosa in pellagrins by means of the gastroscope are those of Schiff and Stevens (13) who reported that the mucosa of the stomach in two patients was similar in appearance to that of the oral cavity. Atrophy of the gastric mucosa is commonly found in human patients dying of pellagra (18). Similar or even closely comparable physical changes are not necessarily to be expected in experimental nicotinic acid deficiency in animals and pellagra in the human subject. The human pellagrin frequently has a deficiency of more than one essential food substance (12, 16, 19). Moreover, the human subject with pellagra suffers from a more prolonged but less complete deficiency of nicotinic acid than occurs in the "acute" animal experiments, and under these conditions it is possible that morphological changes may occur that would not take place in shorter periods.

Gildea, Kattwinkel and Castle (3) were the first to record the effects of lack of the various components of the vitamin B complex upon gastric secretion, as determined by the response to injection of histamine. Their dogs were divided into three groups and placed on diets deficient in 1) the vitamin B complex, 2) vitamin B_1, and 3) the pellagra-preventive factor. Free hydrochloric acid was present in the gastric secretion of every animal, even when the symptoms of the vitamin deficiency were severe. Miller and Rhoads (9) observed that achlorhydria occurred irregularly and only as a late event in canine blacktongue. On the other hand these authors observed that by feeding swine a diet which causes canine blacktongue, a characteristic symptom complex consisting of macrocytic anemia, lesions of the oral mucous membrane, gastric achlorhydria, diarrhea, and motor weakness of the extremities could be produced. In all but one of the latter animals a definite loss of thickness with atrophy of the gastric mucous membrane was apparent. Remissions of the anemia and amelioration of symptoms were induced by the oral or parenteral administration of liver extract; the achlorhydria disappeared after treatment in one case.

Significant interference with acid gastric secretion has been reported in many cases of pellagra, and in other syndromes due to deficiency of vitamins (21). The difficulty of attempting any correlation of the clinical reports with the experimental results in animals is obvious. Aside from the differences due to species variation and types of stimuli, the chief difficulty in comparing the animal with the human observations is that patients with endemic pellagra probably suffer from other nutritional and vitamin deficiencies as well. It is probably incorrect, therefore, to attribute the diminution of acid gastric secretion in pellagrins to the lack of nicotinic acid alone.

SUMMARY

Blacktongue was produced nine times in 5 dogs by means of the Goldberger diet. Although the disease was allowed to become severe in each instance and was accompanied by severe inflammation of the mucosa of the mouth, similar changes were not observed in the gastric mucosa. No significant change in acidity of the gastric secretion occurred in any of the animals during the experiment.

The most characteristic changes noted in the appearance of the gastric mucosa consisted of a mild hyperemia, which usually was present early in the course of the disease and was not associated with the hyperemia and inflammation of the oral mucosa, and a state of decreased tonus of the stomach which facilitated air inflation. Pallor of the gastric mucosa developed in all but one of the animals. In two instances the pallor of the gastric mucosa accompanied a fall in the erythrocyte count and hemoglobin percentage of the blood. No characteristic gross or microscopic changes were observed in the stomach of any of the animals.

Multiple avitaminosis, together with the more gradual development and longer duration of the deficiency state in human pellagrins are circumstances which account for the differences in the manifestations of the naturally occurring and the experimentally produced diseases.

REFERENCES

1. Cowgill, G. R., Deuel, H. J., Jr., Plummer, N., and Messer, F. C.: Amer. Jour. Physiol., 77: 389, 1926.
2. Cramer, W.: Proc. Roy. Soc. Med., Sect. of Trop. Dis. and Parasitology, 27: 473, 1934.
3. Gildea, E. F., Kattwinkel, E. E., and Castle, W. B.: New England Jour. Med., 202: 523, 1930.
4. Goldberger, J., Wheeler, G. A., Lillie, R. D., and Rogers, L. M.: Pub. Health Rep., 43: 657, 1928.
5. Gross, L.: Jour. Path. and Bact., 27: 27, 1924.
6. Hunter, A., Givens, M. H., and Lewis, R. C.: U. S. Public Health Service Hygenic Laboratory Bull. No. 102, pages 39–68, 1916.
7. Layne, John A., and Carey, James B.: Gastroenterology, 1: 690, 1943.
8. McCarrison, R.: Brit. Med. Jour., 2: 36, 1919.
9. Miller, D. K., and Rhoads, C. P.: Jour. Clin. Investig., 14: 153, 1935.
10. Myers, V. C., and Fine, M. S.: Amer. Jour. Med. Sci., 145: 705, 1913.
11. Rhoads, C. P., and Miller, D. K.: Jour. Exper. Med., 58: 585, 1933.
12. Ruffin, J. M., and Smith, D. T.: South. Med. Jour., 32: 40, 1939.
13. Schiff, L., and Stevens, R.: Cited by: Spies, T. D., Bean, W. B., and Ashe, W. F.: Ann. Int. Med., 12: 1830, 1939.
14. Schiödt, E.: Acta med. Scandinav., 84: 456, 1935.
15. Smith, D. T., Persons, E. L., and Harvey, H. I.: Jour. Nutrition, 14: 373, 1937.
16. Spies, T. D., and Aring, C. D.: Jour. Amer. Med. Assn., 110: 1081, 1938.
17. Spies, T. D., and Dowling, A. S.: Amer. Jour. Physiol., 114: 25, 1935.
18. Spies, T. D., and Payne, W.: Jour. Clin. Investig., 12: 229, 1933.
19. Spies, T. D., Vilter, R. W., and Ashe, W. F.: Jour. Amer. Med. Assn., 113: 931, 1939.
20. Turner, R. H.: Jour. Clin. Investig., 10: 61, 1931.
21. Wilbur, D. L.: Amer. Jour. Digest. Dis., 6: 610, 1939.

THE EFFECT OF BILE ACIDS ON THE BILIARY EXCRETION OF CINCHOPHEN[1]

J. H. Annegers, M.S., F. E. Snapp, M.S., A. J. Atkinson, M.D., and A. C. Ivy, M.D.
From the Department of Physiology, Northwestern University Medical School, Chicago

INTRODUCTION

This investigation was undertaken to determine whether the excretion of cinchophen in bile could be increased by feeding bile acids. It is known that cinchophen is excreted by the human and canine liver (1). It is possible that the hepato-toxic action of cinchophen may be decreased by increasing biliary excretion of the drug.

Two types of bile acid preparations which differ in their effect on bile formation were used. *One* was the conjugated, unoxidized cholic acid obtained from cattle bile by precipitation with iron. It contains 50 per cent cholic acid, which is present as sodium glycocholate and taurocholate. Its administration causes a moderate choleresis with an increase in the output of cholates, or of "natural bile salts", or sodium glycocholate and taurocholate. It does not cause a significant increase in blood flow through the hepatic artery (2). This preparation, ("Bilron", Eli Lilly) will be referred to as "ox-bile" acid.

The *other* type of bile acid was an unconjugated, oxidized cholic acid, or dehydrocholic acid. Its administration causes a hydrocholeresis, producing a thin, watery bile without an increase in the output of cholates. It causes an increase in the blood flow through the hepatic artery (2). This preparation will be referred to as dehydrocholic acid, though "Decholin, Sodium" (Riedel de Haen) and "Ketochol" (Searle) were used.

METHODS

Biliary fistula dogs with a duodenal fistula for the return of bile into the intestine were used (3). The dogs were fed a constant diet every 12 hours. The dogs were not used until they had recovered from the operation and were known to produce a constant output of bile and cholic acid under basal conditions of the diet with and without the return of bile or the feeding of bile salts. Results were discarded if the animal refused food, vomited, or developed diarrhea, because these factors are known to influence bile formation.

Cinchophen determinations were made by Bradley's method (4).

RESULTS

A. Excretion of Cinchophen when no bile acids are given; the control experiment. The animals were fed the diet every 12 hours. No bile or bile acids were re-

[1] This study was assisted by a grant from E. L. Dawes and Marjorie Newman.

turned to the intestine. When a basal output was obtained, 500 mg. of cinchophen was given with each meal, or 1.0 gm. daily, for three days. Cinchophen analyses were made daily. The average 24 hour output only is shown in table 1.

The results are shown in column A, table 1. Note that in the 13 tests on 6 dogs an average of 43 per cent of the cinchophen administered daily was recovered. The biliary cinchophen in the individual tests ranged from 28 to 52 per cent.

TABLE 1

The effect of conjugated, unoxidized ("ox-bile") and of unconjugated, oxidized (dehydrocholic acid) cholic acid on the excretion of Cinchophen in the bile

DOG	A			B				C			
	500 mg. cinchophen every 12 hours										
	Control, no bile acids			3 gm. "ox-bile" daily				3 gm. dehydrocholic acid daily			
	Vol. in cc.	mg. cinch.	% of dose	Vol. in cc.	mg. cinch.	% of dose	% change	Vol. in cc.	mg. cinch.	% of dose	% change
B-8	222	457	48					300	617	62	+35
B-10	224	386	39	291	458	46	+19	373	477	48	+24
B-10	169	284	28	346	490	49	+72	314	370	37	+30
B-10	267	488	49	308	533	53	+9				
B-10	206	393	39	250	465	47	+18				
C-4	257	489	49	353	593	59	+21	391	488	49	0
C-7	281	393	39	345	464	46	+18	490	473	37	+20
C-7	278	415	42	404	482	48	+16	422	498	50	+20
C-7	289	440	44	334	509	51	+16				
C-7	271	385	39	323	491	49	+28	344	481	48	+25
C-8	329	524	52	350	546	55	+4	385	545	55	+4
C-8	361	524	52					462	521	52	0
C-10	241	442	44	315	438	44	0	469	509	51	+15
Ave.....	261	432	43	329*	497	50	+15	395†	498	49	+15

* 26 per cent increase over control col. A.

† 51 per cent increase over control col. A.

B. Excretion of Cinchophen when conjugated, unoxidized bile acids ("ox-bile" or Bilron) were given. The same experimental regime as in "A" above was used, except that 1.5 gm. of "ox-bile" acid was given every 12 hours in addition to 500 mg. of cinchophen.

The results are shown in column B, table 1. The average daily recovery of cinchophen in the bile was 50 per cent of the 24 hour dose. Thus, the daily administration of "ox-bile" acid was associated with an average increase of 20 per cent (15 per cent when the output of the group is pooled) in the excretion of cinchophen as compared with the control. An increased excretion

occurred in every test but one. Statistical analysis showed that the increase over the control was significant, or not due to chance or to random sampling.

C. Excretion of Cinchophen when unconjugated, oxidized cholic acid (dehydrocholic acid, Decholin or Ketochol) was given. The same experimental procedure as in "B" above was used, except that 1.5 gm. of sodium dehydrocholate was given every 12 hours together with 500 mg. of cinchophen.

The results are shown in column C, table 1. The average recovery of cinchophen in 24 hours was again about 50 per cent of the daily dose of 1.0 gm. The daily feeding of 3.0 gm. of dehydrocholate was thus associated with an average increase of 17 per cent (15 per cent when the output of the group is pooled) in the excretion of cinchophen as compared with the control. This increase was statistically significant. However "ox-bile" caused as much increase in the excretion of cinchophen as did dehydrocholic acid.

DISCUSSION

It is well established that cinchophen, sodium dehydrocholate, and the salts of "ox-bile" acids cause a choleresis. A hydrocholeresis is produced by cinchophen and sodium dehydrocholate; these substances also increase hepatic arterial blood flow. "Ox-bile" acid causes a moderate choleresis but no change in hepatic arterial flow. Referring to table 1, it will be noted that "ox-bile" acid produced an average increase of 26 per cent (column B) and dehydrocholic acid an average increase of 51 per cent (column C) in volume output over that caused by cinchophen alone (column A). Cinchophen, of course, was given during the control period as well as with both bile acid preparations. Thus there are *two* choleretic agents (cinchophen and bile acid) stimulating the liver in the series of tests shown in columns B and C (table 1).

The results show that the liver in the absence of bile acids can excrete an average of 43 per cent of a dose of cinchophen in 24 hours. Moderate choleresis can increase this excretion, but a limit is reached beyond which further choleresis will not increase cinchophen excretion in the bile.

It must be remembered that the normal liver is never deprived of bile acids as was that of the animals in the control group. Hence, in the intact animal whose liver is being stimulated by its own bile acids, it may be superfluous to administer additional bile acid, especially since cinchophen is such a good hydrocholeretic per se.

There are other factors besides a moderate choleresis which may have facilitated cinchophen excretion when bile acids were fed. It is possible that cinchophen is more soluble in the bile produced by giving bile acids, or that the cinchophen combines with the bile acids in some manner.

The results do not answer the question: Does an increase in hepatic arterial blood flow increase cinchophen excretion? Cinchophen itself increases hepatic

arterial blood flow, and there is no evidence that sodium dehydrocholate has an additive effect together with cinchophen in regard to this action. It may be that an increase in hepatic arterial blood flow may act to decrease the toxic effect of cinchophen on the liver; this question, however, will have to be answered by a different experimental approach from that pursued in this study.

Although these results do not show that the toxicity of cinchophen may be decreased by the simultaneous administration of bile salts, they, along with the results of other studies (1, 5, 6), indicate that a direct experiment to settle the question should be undertaken.

CONCLUSIONS

1. A moderate choleresis produced by sodium glycocholate and taurocholate, and a more marked choleresis produced by sodium dehydrocholate were associated with equal increases in the excretion of cincophen in the bile of chronic biliary fistula dogs.

2. The biliary excretion of cinchophen is not directly proportional to the bile volume output.

REFERENCES

1. Annegers, J. H., Snapp, F. E., Ivy, A. C., Atkinson, A. J., and Berman, A. L.: Gastroenterology, 1: 597, 1943.
2. Grodins, F. S., Osborne, S. L., Ivy, A. C., and Goldman, L.: Am. J. Physiol., 132: 375, 1941.
3. Kocour, E., and Ivy, A. C.: Am. J. Physiol., 122: 325, 1938.
4. Bradley, W. B., and Ivy, A. C.: Proc. Soc. Exp. Biol. Med., 45: 143, 1940.
5. Berman, A. L., Snapp, E. F., Atkinson, A. J., and Ivy, A. C.: J. Lab. Clin. Med., 28: 682, 1943.
6. Annegers, J. H., Snapp, F. E., Atkinson, A. J., and Ivy, A. C.: J. Lab. Clin. Med., 28: 828, 1943.

EDITORIALS

THE WISDOM OF MEASURING THE LIVER FUNCTION BEFORE OPERATING FOR CANCER IN THE ABDOMEN

There would seem to be little use in removing a cancer of the stomach when the peritoneum on the rectal shelf or the lymph nodes in the left supraclavicular space are full of the disease, and there can be little use in removing a cancer of the colon when the liver is heavily involved. In such case the patient's life is not likely to be prolonged by resection of the original growth, and then the repute of the surgeon, and of the institution in which he works, and even of the whole art of surgery may suffer injury.

Often, when at necropsy on patients recently operated on for cancer of the digestive tract one finds the liver full of metastatic nodules, one cannot help wondering why the patient's family couldn't have been spared much expense and the surgeon some chagrin by the preoperative demonstration that there was no chance for an operation to work a cure.

Because the invasion of the liver by cancer brings impairment of the functions of this organ, and since in many cases this impairment can easily be detected by an appropriate test, it would seem that such a test should be a routine procedure in all cases in which it is a question whether or not an abdominal cancer has metastasized.

In those cases in which only a slight failure in liver function can be demonstrated, and the lesion looks operable with the roentgen ray, it may be well to give the patient his chance and let him have the abdomen explored, but in those cases in which the liver is evidently much damaged, it would seem best to refuse operation unless this seems necessary to avoid death due to starvation or intestinal obstruction.

WALTER C. ALVAREZ

INSOMNIA AND DIARRHEA DUE TO EXCESSIVE WATER DRINKING

Now that so many dietitians and some physicians are ordering all their patients to drink an extra, unwanted and probably unneeded dozen or more glasses of water a day the physician who is on the watch can find an occasional case of insomnia in which the patient's rest is being broken by his having to get up several times at night to rid himself of the extra fluid. Occasionally, also, one will find a patient with a diarrhea which is due to the rapid flushing of food down the bowel by the excessive amount of fluid ingested. Probably in most cases of apparently functional diarrhea the physician should inquire as to the amount of water being drunk.

Actually, one cannot help questioning the wisdom of giving unwanted water to everyone. Physiologists tell us that a person's thirst, except in the presence of profuse perspiration, always apprises him of the exact amount of water which his body needs at the time and to take more than this can only add to the work of the organs that must move the fluid around and get rid of it. The drinking of extra water may help some persons to conquer constipation, but in many cases it cannot be counted on to have any such beneficial effect.

WALTER C. ALVAREZ

FREDERICK H. KRUSE

Frederick Herman Kruse, clinical professor of medicine at the University of California Medical School and an active member of the American Gastro-enterological Association, died at his home in San Francisco on January 14, 1943.

Dr. Kruse was born in Milburn, Kentucky on June 30, 1879. Both of his grandfathers were physicians. He graduated from high school in Tulare, California where he was on the football and track teams. He attended the University of California from 1902 until 1904 when he was forced to leave his studies in order to contribute to the support of his family after the death of his father.

Dr. Kruse became a teacher of Latin in the Alameda School System and after several years rose to the position of principal of the Alameda High School. As soon as possible he returned to his studies at the University of California and graduated from the Medical School in 1915. He accepted an internship in medicine at the University of California Hospital after which he became assistant resident in medicine at the Johns Hopkins Hospital on Dr. Barker's service. Later he was resident physician at the Bayview Hospital in Baltimore. On August 25, 1917, he married Miss Gertrude Eabes, the daughter of a physician, and a graduate nurse in her own right.

After the completion of his training in Baltimore, Dr. Kruse returned to San Francisco where he became an associate in the office of Dr. H. C. Moffitt, and later in the office of Dr. Walter C. Alvarez. Shortly after he started on his own. His practice grew so large that he needed two assistants.

Dr. Kruse took a lively interest in academic medicine. He commenced as an assistant in medicine at the University of California Medical School and rose to the clinical professorship of medicine in 1930. At one time he was in charge of the University of California Medical Clinic. In 1931 he became chief of the gastro-intestinal unit and kept this post until his death. The problems which intrigued him most were complications of peptic ulcer and functional disorders of the colon. Everything that Dr. Kruse did carried the imprint of his faculty

for taking infinite pains. Aside from his work, Dr. Kruse's life was devoted to his family consisting of his wife and two daughters. He cared little for social activities, but preferred to spend any available time at his place in the Sierra Nevada mountains.

Dr. Kruse's death at the height of his successful career constitutes an irreparable loss to his family, friends, patients, students and colleagues.

THEODORE L. ALTHAUSEN

AMERICAN GASTROENTEROLOGICAL ASSOCIATION

List of Members in Active Service as of Jan. 22, 1944

BANK, JOSEPH
BARRON, LOUIS E., (Captain) M.C., Kennedy General Hospital, Memphis 15, Tennessee
BERGH, GEORGE S., (Major) M.C., 2420 West 24th Street, Minneapolis, Minnesota
BERK, J. EDWARD, (Captain) M.C., 1257 SCSU, Tilton General Hospital, Fort Dix, N. J.
BERCOVITZ, ZACHARIAS, 0209820, APO 4135, % Postmaster, New York, New York
BORLAND, JAMES L., (Major) M.C., 0-441695, APO 923, % Postmaster, San Francisco, California
BROWN, PHILIP W., 0245297, APO 9128, % Postmaster, San Francisco, California
BUTT, H. R., (Lt.) M.C.-V(S), U.S.N.R., % Naval Hospital, Corona, California
CHAMBERLIN, DONALD T., (Major), 306th Station Hospital, Camp McCoy, Wisconsin
FAUST, D. B., % D. E. Crandall, 1810 F Street, Vancouver, Washington
FERGUSON, LEWIS K.
FLOOD, CHARLES A., 410 Riverside Drive, New York, New York
GLENN, P. M., APO 924, % Postmaster, San Francisco, California
JOHNSON, THOMAS A.
KANTOR, JOHN L., (Col.), Headquarters 49th Gen'l. Hospital, Borden Gen'l. Hospital, Chickasha, Oklahoma
KRAEMER, MANFRED, (Major), Station Hospital, Jefferson Barracks, Missouri
LAYNE, JOHN A. (1st Lt.—Army)
MACHELLA, C. E., Univ. of Pa., Phil., Pa. (Now serving with Univ. Hospital in India.)
MACKIE, T. T., (Lt. Col.), Army Medical Center, Washington, D. C.
McIVER, M. A., Basset Hospital, Cooperstown, N. Y. (Overseas in 33rd Gen. Hospital)
MEYERS, FRANK, (Major), 36 Walton Drive, Snyder, New York
MORRISON, SAMUEL, (Major), Valley Forge General Hospital, Phoenixville, Pa.
OVERSTREET, SAMUEL
ROSENAK, B. D., (Captain), 0-460250, U. S. Army, APO 612, N. Y. C.
ROSENBERG, DAVID H., (Lt. Comdr.) U.S.N.R., 310 So. Michigan Avenue, Chicago, Ill.
SNELL, ALBERT M., (Comdr.) M.C.-V(S), % Postmaster, San Francisco, California
SULLIVAN, ALBERT J., (Major), Army Air Force, Station Hospital, Miami Beach, Fla.
TWISS, JOHN R., (Comdr.) M.C., U.S.N.R.
WILBUR, DWIGHT L., U.S.N.R., U. S. Naval Hospital, Shoemaker, California
WILLARD, JOHN H., 232 Jefferson Street, E. Greenville, Pennsylvania
WIRTS, C. W., 0104560, APO 678, % Postmaster, New York, New York
ZOLLINGER, ROBERT, Peter Bent Brigham Hospital, Boston, Mass.

BOOK REVIEWS

Nervousness, Indigestion and Pain. By WALTER C. ALVAREZ. Paul B. Hoeber, Inc. Published 1943.

Dr. Alvarez renowned for his work in experimental physiology of the alimentary tract, a mature and experienced clinician, is now Consultant in the Division of Medicine at the Mayo Clinic. He gives here of his accumulated wisdom and years of knowledge to us of the medical profession, on a subject familiar to us all and yet insufficiently dealt with in current literature.

In this book devoted to the functional or neurotic individual suffering from the common complaints of nervousness and pain, the psychology of the patient, his personality and psychic make-up are matched against the personality of the physician whose task it is to analyze the confused symptoms of the abdominal complaints. The shelves of libraries are stacked with books of great maturity on straight-forward clinical medicine; the files are filled with laboratory work, experimental and physiological; the complicated phases of psychoanalysis which few practitioners can understand or practice have covered the subject, but nowhere with equal brilliancy, in a manner direct and conversational has any one, in recent years, addressed himself to the difficult task of analyzing, understanding and treating the purely nervous patient with his multitudinous subjective symptoms. It would take a man of Dr. Alvarez's charming and open personality, with the extensive fervor, and experience of forty years, dealing direct with the innumerable sick, to give so succinct and understandable an analysis of the sick mind, the confused spiritual state of the neurotic patient, his social and personal problems, his conflicts and inhibitions. As he states in this book, only the physician who has human understanding and sympathy can elicit the cooperation and confidence of the patient. In the very important chapter on History Taking, he emphasizes the need for the patient to be attracted by the warm humanity of the physician, in order that he may recognize a kindred soul who is capable of understanding and sympathizing with his complaints.

Nowhere in the book will one find the discussion of the id and the libido and the ano-erotic fantasies, and for this the book may be criticized by the professional psychoanalists. But psychoanalysis would be impossible for the thousands of neurotics one sees in the practice of gastroenterology, impossible because of the limitation of funds and of time.

On the other hand the practice of making diagnoses from elaborate complicated and often unnecessary laboratory reports, devoid of clinical interest or significance, is exposed as futile, often misleading, and lacking in the essential clinical import which the older generation of practitioners possessed as a sixth sense. Such falderals as pseudo-ulcer, chronic appendicitis, ureteral kinks, intestinal intoxication are properly de-evaluated. Dr. Alvarez approaches his patient as a human being, who backed by a world of clinical knowledge, sees quickly into the constitutional inadequacy of his patient, his problems, his fears, the aborted love life, the economic insufficiencies, the thousands of personal entanglements and problems which are expressed by the sick one in terms of nervousness, of pain, of indigestion. The sizing up of the personality of the patient, the handling of the nervous one; when one

is to tell the truth to the patient, how to prescribe the proper laboratory studies and when to spare the sufferer unnecessary expense; constitutional inadequacy, the nervous breakdown and its causes, and above all the treatment of the psychopathic, poorly adjusted, much troubled, tired persons; these are among the topics which receive the attention from a person of great understanding.

What DuBois and S. Weir Mitchell did for the past generation in the care of the neurasthenic, Alvarez has again done for us, this time with all the advantages of Freud and of psychoanalysis, and what it has taught us; this time, for us who practice abdominal medicine as a specialty, he has concentrated on the care and treatment of the abdominal neurasthenic.

The style of the book is direct and forceful; words are not minced when it is essential to confound evil practices or popular mistakes. We recognize as we read its chapters and its many case histories our own innumerable neurotics whom we have met in practice, and we see how much better he has understood them, how quickly he has gained their confidence and their friendship, how ably he has advised them, how immeasurably he has helped them. The years the author has spent in the laboratories of experimental physiology have stood him in good stead in interpreting symptoms. The years that he has practiced medicine as a consultant, and at the bedside, his wide erudition in medicine and its allied sciences, has given him a universal interest in things human. His wide knowledge of world literature, his natural culture and charm, his genial smile, and above all his sense of humor lend a radiance to the book which enhances its import and its content.

This review of the book on nervousness, indigestion and pain may seem fulsome praise; it is however well merited praise due to a fine scientific and literary effort.

BURRILL B. CROHN

A Hundred Years of Medicine. By C. D. HAAGENSEN and WYNDHAM, E. B. LLOYD. 443 pp. Sheridan House, New York, 1943. Price: $3.75.

This is a fine book for either layman or physician. It is full of information and interestingly written. It can be of interest even to someone who is fairly conversant with the history of medicine.

The book is divided into four parts on (1) Medicine up to a hundred years ago; (2) Medical science during the last hundred years; (3) Surgery during the last hundred years, and (4) New social aspects of Medicine.

There are interesting chapters on such subjects as the sanitary conditions of the people a hundred years ago, some common infectious diseases of a century ago, and the development of knowledge in regard to diabetes, pernicious anemia, and other diseases. The authors have given a series of pen pictures of episodes and major discoveries in medicine and have not tried to cover the whole field as Fielding Garrison did.

An Introduction to Foods and Nutrition. By H. C. SHERMAN and C. S. SANFORD. 292 pp. Macmillan, New York, 1943. $2.00.

This attractive book looks like an excellent text for nurses or dietitians or medical students. It has the advantage of combining briefness with authoritativeness which is just what every student wants.

ABSTRACTS OF CURRENT LITERATURE

FRANKLIN HOLLANDER

Associate Editor in Charge of Abstracts
Mount Sinai Hospital, New York City

STAFF OF ABSTRACTORS

ALBERT CORNELL, New York, N. Y.
MAURICE FELDMAN, Baltimore, Md.
*CHARLES A. FLOOD, New York, N. Y.
M. H. F. FRIEDMAN, Philadelphia, Pa.
IRVING GRAY, Brooklyn, N. Y.
*J. DUFFY HANCOCK, Louisville, Ky.
MANFRED HESS, New York, N. Y.
*THOMAS A. JOHNSON, Philadelphia, Pa.
ALLEN A. JONES, Buffalo, N. Y.
N. W. JONES, Portland, Ore.
*JOSEPH B. KIRSNER, Chicago, Ill.
*HENRY H. LERNER, Boston, Mass.
PHILLIP LEVITSKY, Montreal, Can.
*JESSHIL LOVE, Louisville, Ky.
FRANZ J. LUST, New York, N. Y.
ARTHUR E. MEYER, Flushing, N. Y.
FRANCIS D. MURPHY, Milwaukee, Wis.
H. NECHELES, Chicago, Ill.
FRANK NEUWELT, Gary, Indiana
*SAM OVERSTREET, Louisville, Ky.
DAVID J. SANDWEISS, Detroit, Mich.
MICHAEL W. SHUTKIN, Milwaukee, Wis.
VIRGIL E. SIMPSON, Louisville, Ky.
H. J. SIMS, Denver, Colo.
HENRY TUMEN, Philadelphia, Pa.
*ROBERT TURELL, New York, N. Y.
*EDGAR WAYBURN, San Francisco, Cal.
*JOHN H. WILLARD, Philadelphia, Pa
*C. WILMER WIRTS, Philadelphia, Pa.
*IRVING J. WOLMAN, Philadelphia, Pa.

*In Military Service

[Microfilm copies of papers may be obtained from Microfilm Service of the Army Medical Library at 25 cents for each complete article, not exceeding 25 pages in length, and 10 cents for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittance may be made with subsequent orders and in such a manner as found convenient. Address: Microfilm Service, Army Medical Library, Washington, D. C.]

MOUTH AND ESOPHAGUS

SMITHERS, D. W., CLARKSON, J. R., AND STRONG, J. A. The roentgen treatment of cancer of the esophagus. Am. J. Roent. Rad. Therapy, 49: 606 (May) 1943.

The authors believe that Roentgen treatment of carcinoma of the esophagus should be more successful now than in the past. Four reasons are given for failure of treatment: (1) advanced stage of the disease, (2) relation to vital structures with perforation, (3) the high grade of malignancy, and (4) starvation. Following adequate therapy, much can be done to relieve symptoms and prolong life, especially by way of adequate nourishment. A discussion of the various forms of therapy is given. The authors point out that the surgical removal of esophageal tumors causes a high operative mortality and is applicable in but a few cases. The implantation of radon cannot be adequately carried out, owing to the difficulty of placement of this form of treatment. Best results have so far been attained by the radium bougie, but the disadvantage is the difficulty of passing the upper limits of the obstruction, as well as the local trauma with risk of perforation. However, Roentgen therapy has much to be recommended, and it is the most effective method of therapy. A detailed description of the Roentgen method of treatment is given. The classification, preparation of patient, selection of treatment fields, localization in beam direction, scheme of irradiation, and the after care of the patient are all discussed. The results of treatment of the different sections of the esophagus, and also those involving the stomach, are given in 44 cases. A study of the distribution of the dosage throughout the irradiated volume in certain selected methods of Roentgen ray therapy is discussed. The application of these rays is well illustrated. There were 20 cases treated over a period of 6 months, 15 of which were completed. Of these, there was one with no relief of symptoms, 7

with symptoms partially relieved and 7 free from symptoms.

MAURICE FELDMAN.

STOMACH

BABKIN, B. P., ARMOUR, J. C., AND WEBSTER, D. R. Restoration of the functional capacity of the stomach when deprived of its main arterial blood supply. Can. Med. Ass. J., 48: 1 (Jan.) 1943.

The central theme of this address is the reaction of the stomach to the diminution of its arterial blood supply, and also the effect of obstruction to the circulation in other organs such as the heart and brain. A lasting improvement of restricted circulation can be achieved only through the development of a collateral circulation. Oppel and Fauteux had observed that, upon venous ligation in the case of occlusion of an artery (in an extremity or in the heart), benefit was derived because of a rise in venous and arterial blood pressure in the vascular bed peripheral to the obstruction, and also the development of a collateral circulation. The work of Oppel with the circulation of the leg, of Fauteux with that of the heart, of Andreyev with the brain, have been extended by the present authors to the stomach with similar results.

The stomach differs radically from the brain in that a drastic reduction has little effect on its function. The problem of partial or total devascularization poses the following questions to the surgeon: (1) Is it permissible, in the case of a gastric hemorrhage, to tie the gastric arteries nearest to the bleeding? (2) Would not such radical interference with the arterial circulation of the stomach produce necrosis in the surrounding wall? (3) Would it not be possible by partial devascularization of the stomach to diminish the production of acid gastric juice and thus facilitate the healing of a peptic ulcer? (4) Would not the mass destruction of the nerves going to the stomach in the vascular walls diminish its secretory function?

The authors performed 3 series of experiments: total devascularization of the stomach, ligation of the main gastric arteries, and ligation of the gastric arteries and its effect on gastric secretion. All dogs of the first series died within 3 days; their stomachs were swollen, necrotic and perforated. In the second series, the animals all showed no ill effects; autopsy and experimental results justified the conclusion that this type of ligation is a dangerous procedure and may result in the formation of localized foci of gangrenous degeneration in the gastric mucosa. But the stomach was still able to secrete an acid gastric juice. The dogs of the third series all quickly recovered from the operation; in some instances the volume of gastric juice secreted in response to sham feeding or to histamine was reduced—in others it was increased. One month after the operation, gastric secretory response was normal. There was hardly any change in the free and total acidities or the total chloride concentration. Some diminution of the peptic power resulted, especially after sham feeding. The gastric mucosa was undamaged. The motor function of the stomach did not suffer appreciably. The procedures followed with the last two series of animals does not completely deprive the stomach of its arterial circulation, as a result of multiple anastomoses between the left gastric artery and the branches of the phrenic and esophageal arteries. All the organs surrounding the stomach participated in the revascularization. The various factors which may be concerned in the formation of a collateral circulation are discussed.

IRA A. MANVILLE.

COX, A. J. The stomach in pernicious anemia. Am. J. Path., 19: 491 (May) 1943.

The stomachs of 6 patients dying of pernicious anemia were studied within a few hours after death—in order to corroborate, if possible, the reported evidence that the "intrinsic factor" is produced in the fundus and body of that organ. After fixation in 4 per cent solution of formaldehyde the mucosa was removed in long strips extending the entire lengths of the greater and lesser curvatures. These strips were then rolled "like a fire hose", imbedded in paraffin, and sectioned uniformly in a plane perpendicular to the surface, so that uniform relations were obtained. Two of the pa-

tients had been successfully controlled by liver therapy for 13 and 10 years respectively and the remaining 4 patients had had little or no treatment.

The histological appearance of the mucosa was essentially the same in the treated and untreated cases: the changes in the fundus were extensive and severe. The mucosa was but half the thickness of that of the pyloric zone. The normal mucosal glands of the fundic type were largely replaced by scattered undifferentiated glands. The chief and parietal cells were almost completely absent. Only in one case in which liver therapy had been maintained during life were there a few scattered groups of atypical glands with a few cells resembling parietal cells, seen along the upper portion of the lesser curvature; chief cells were absent. Groups and single glands, resembling mucosal glands of the small intestine, were found scattered about. Goblet and Paneth cells were numerous. Among these were seen some interstitial cells which resembled lymphocytes and plasma cells. There were no distinguishing changes found in the mucosa of the pyloric zone and the mucosa was considered essentially normal.

The stomach from one case of non-tropical sprue showed none of the changes which characterized the stomachs of the pernicious anemia cases. The bone marrow, however, contained many cells morphologically similar to the megaloblasts of pernicious anemia. The author suggests, because the gastric lesions in these cases of pernicious anemia were all alike and were different from those accompanying other diseases, that they may represent a specific change, perhaps the result of massive destruction of the highly differentiated parietal and chief cells.

N. W. JONES.

BOWEL

KUITUNEN-EKBAUM, E. The incidence of enterobiasis in Toronto. Can. Med. Ass. J., 48: 229 (Mar.) 1943.

The present report gives the results of examination of 300 children and 56 adults in Toronto homes and constitutes the first survey made in Toronto of enterobiasis in non-hospitalized individuals. The NIH swab was used in diagnosis. In all, 2,174 swabs were taken, an average of 6 per person. Sixty per cent of the children and 52 per cent of the adults were found to be infected with pinworms. The highest incidence of enterobiasis occurred in the age group 6–11 years, and the incidence was higher in girls than in boys. These results are regarded as showing a high incidence of enterobiasis in Toronto. Earlier surveys showed that 48 per cent of 843 hospitalized children and 9.8 per cent of adults were infected. These figures are regarded as being lower than what actually might be found, due to the fact that not over 3 swabs per person were employed. This survey also shows the familial nature of pin worm infection.

IRA A. MANVILLE

INGELFINGER, F. J. AND MOSS, R. E. The motility of the small intestine in sprue. J. Clin. Invest., 22: 345 (May) 1943

Ingelfinger and Moss repeatedly intubated 2 patients with sprue and studied the motor activity of the small intestine by means of the balloon-kymograph method. When the standard balloon is placed under a pressure averaging 20 cm. of water, it accommodates less than 30 cc. of air. In one of the cases studied a pressure of 5 to 9 cm. of water was sufficient to inflate the balloon with 75 cc. of air, in the other 10 to 15 cm. of water maintained 45 cc. of air in the balloon. The large waves found in records of the normal were absent; the small waves were smaller than those usually seen. Treatment with individual fractions of the vitamin B complex produced little change in the tracings. Prolonged treatment with whole vitamin B complex produced some improvement in the records, which, however, was not commensurate with the clinical results obtained. Injection of acetyl-beta-methylcholine chloride stimulated the intestinal motility of both patients; prostigmine was without effect. In 1 patient posterior-pituitary solution, adrenal cortical extract, and desoxycorticosterone produced no changes. These observations suggested to the authors that in sprue the nervous apparatus of the small intestine fails to liberate active acetylcholine.

CAPT. EDGAR WAYBURN

WARD, C. S., AND COOPER, F. W. Atresia of the duodenum. Ann. Surg., 117: 718 (May) 1943.

A case of complete atresia of the duodenum is presented as the fifteenth successfully operated case to be reported in the literature. A female infant was shown to have obstruction beyond the proximal duodenum. The infant was operated upon at 5 days of age and complete atresia of part of the second portion of the duodenum found, probably beyond the ampulla of Vater. An anastomosis was formed between the end of the dilated second portion of the duodenum and the side of the third portion The infant had a smooth postoperative course and at the end of 3 months was developing normally. In all previous successful cases of duodenal atresia either gastroenterostomy or duodenojejunostomy had been done, depending upon whether or not the bile ducts were below or above the atresic site. This is the only case in which duodeno-duodenostomy was performed.

FRANK NEUWELT

FOLLEY, J. H. The medical management of intestinal obstruction. New Engl. J. Med., 228: 606 (May) 1943.

Intestinal obstruction without strangulation does not necessarily represent a surgical emergency. Nonsurgical methods of decompression done in conjunction with surgery have reduced the mortality rate from 30 to 10 per cent or less. Distention of the bowel is recognized as the factor initiating the physiologic and chemical changes which occur in intestinal obstruction. The intelligent use of intravenous fluids and transfusions is effective in combatting these changes temporarily. Initially, the usual fluid requirement is at least 3 liters; the infusions may consist of physiologic saline solution or 5 per cent glucose in salt solution or in distilled water. Sodium lactate solution may be given to correct acidosis if present. Relief of the bowel distention is of primary importance and is best accomplished by intestinal intubation. By this method it is possible to measure accurately the fluid and electrolyte loss into the bowel lumen. The obstructive lesion may be definitely located, and in many cases its nature determined. Most important is the fact that, since the intubated patient may be fed a low residue diet, nutrition may be maintained almost indefinitely, making the time of operation, if necessary, elective. In any case of intestinal obstruction the decision is not whether it should be treated medically or surgically but whether it should be treated medically or surgically at the particular time the patient is seen. The author presents an excellent exposition of the technic of introducing the Miller-Abbott tube.

JOSEPH B. KIRSNER.

LIVER AND GALLBLADDER

OTTENBERG, R. Bilirubin and bile salts in jaundice. J. Mount Sinai Hosp., 9: 937 (Mar.–Apr.) 1943.

An excellent discussion of this subject in simple terms is given by the author. The chemistry and properties of bilirubin, its relation to porphyrins and hemins, its detection and measurement in blood are included. The differences between direct and indirect Van den Bergh reactions are both quantitative and qualitative, and their great clinical importance is shown in the tables accompanying the article. The direct action is obtained only in liver diseases and obstructions of the bile ducts. The indirect action is given by normal serum and hemolytic diseases. However, from a quantitative point of view, the Van den Bergh test is unreliable, being little more accurate than the much simpler icteric index. The photo-electric colorimeter gives more precise results and measures direct and indirect reacting bilirubin exactly in all varieties of jaundice. Bilirubin is derived from hemoglobin and its analogue in the muscles, myoglobin. The reticulo-endothelial tissues are responsible for the conversion. The parenchymal liver cells absorb the bilirubin from the blood stream and excrete it. The bilirubin excretion test after intravenous injection is the most delicate test of liver function in the absence of jaundice, but it is expensive and impractical. In regard to the quantity of bilirubin in the blood, a single test is of little significance but a series of tests giving a curve is of great value.

Unlike bilirubin, which is a mere excretion product, bile salts are powerful substances which are indispensable to life. The real function of the secretion of bile is to bring the salts into the intestines. The absorption of essential lipoids, calcium, and vitamins depends on the presence of bile salts. The chemical and physical properties of the latter are given in diagrams. The secretions and internal circulation of bile salts and their therapeutic use are also explained. The bile salt load test of Josephson, which may become a valuable diagnostic method, and the modern concept of pathogenesis of jaundice, conclude the paper.

ALBERT CORNELL.

MACDONALD, D. The indications for common duct exploration. Can. Med. Ass. J., 48: 341 (Apr.) 1943.

In diseases of the biliary system, the extrahepatic ductal system plays an important role. Biliary disease presents a most complex problem. Residual disease of the ductal system is the most common cause of lack of improvement following cholecystectomy. Biliary disease is progressive and may result in a danger more serious than the original gall-bladder trouble. The higher mortality of secondary operations is due to complications arising from bile tract disease which, for the most part, are those of common duct origin. Every primary gall-bladder operation should be regarded as a potential duct exploration especially if bladder stones were diagnosed pre-operatively. Reduction of the incidence of common duct calculi will lessen the occurrence of symptoms following cholecystectomy. No operator should regard a cholecystectomy as "simple". He should look for and be able to recognize and adequately treat associated abnormalities.

The author discusses the indications for opening, exploring and perfusing the common duct. These are segregated into the indications as determined before operation and those as determined at operation. Among the former are: a history of jaundice; involuntary attacks of vomiting with the attacks of colic; an increasing frequency of attacks; Charcot's so-called syndrome of colic, fever, chills, and jaundice; persistence of biliary fistula following operation; symptoms following cholecystectomy which demand operation; and chronic non-calculus cholecystitis. Among the latter are listed: the presence of lesions which necessitate perfusion; the palpation of stones in the common duct; a distended or thickened duct; a small fibrosed gall bladder, particularly if the cystic duct is dilated; the presence of many small bladder stones; aspirated bile from the common duct showing a cloudy or hazy appearance; and enlarged or otherwise pathological pancreas and a pathological liver.

The question of medical or surgical treatment for acute cholecystitis is a debatable one; some favour conservative and others radical treatment. One of the better arguments against radical treatment is that the common duct cannot be properly explored. The writer advocates a two-stage procedure for certain cases of acute cholecystitis. The first stage is simple and quick drainage, the second, removal and probably ductal surgery. The advantages of these are given.

IRA A. MANVILLE.

BERNHART, F. W., AND SCHNEIDER, R. W. A new test of liver function—the tyrosine tolerance test. Am. J. Med. Sci., 205: 636 (May) 1943.

The writers state that impairment of amino acid metabolism in hepatic disease was probably first suggested by Frerichs who noticed the presence of tyrosine and leucine crystals in the urine in cases of acute yellow atrophy. Lichtman found a quantitative increase of tyrosinuria in various liver diseases. Jankelson was unable to detect tyrosine in normal blood but found it in a high percentage of patients with liver disease. The writers used a modification of the Millon reaction in testing for blood tyrosil. They used a photoelectric colorimeter and found a concentration of tyrosil in the normal fasting blood equivalent of 1 to 1.8 mg. of tyrosine per 100 cc. of blood. In testing 10 normal subjects, the average fasting tyrosil was 1.4 mg./100 cc. They gave 4 gm. of tyrosine to each subject and found an average concentration of 5.4 in 1 hour, 4.6 in 2 hours, and 3.4 mg. per 100

cc. in 3 hours. The tyrosine tolerance test was then done in cases of liver disease and it was found that "in every instance of cirrhosis of the liver thus far studied the tolerance to orally ingested tyrosine was diminished. In some patients levels as high as 15 mg. were found 1 hour after consumption; furthermore, the hypertyrosinemia persisted at levels as high as 8 to 11 mg. for as long as 3½ hours after ingestion of the substance." The authors used the tyrosine test in non-cirrhotic hepatic disease including diabetes, rheumatoid arthritis, chronic cholecystitis and stones, carcinoma of the common bile duct with a normal preoperative galactose tolerance test, acute cholecystitis with normal hippuric acid tests on 2 occasions, and a case of hepatocellular jaundice with icterus index of 80. The tyrosine was mildly positive in 7 cases of non-cirrhotic hepatic disease. The writers then studied the test in a group of 8 cases with non-hepatic disease and found no evidence of impaired tyrosine tolerance in 6 while 2 had slight elevations over the normal.

ALLEN A. JONES.

BOLES, R. S. Alcohol and cirrhosis of the liver. Southern Med. J., 36: 353 (May) 1943.

Experimental efforts to produce cirrhosis of the liver by means of alcohol alone have not been successful. It is probable that such influence as alcohol exerts in causing human cirrhosis results from its action in reinforcing or accentuating the effects of other agents, or in producing degenerative changes in the hepatic cells, thereby rendering them more susceptible to injury. Deficiencies of carbohydrate, protein, and the vitamin B complex which occur frequently alcoholics constitute more important factors in the development of hepatic cirrhosis. Detailed analyses of large series of autopsy cases have disclosed that fatty metamorphosis of the liver and portal cirrhosis, as well as all other types of cirrhosis, occurred twice as often in non-alcoholics as in alcoholics. Indeed, the portal type of cirrhosis, which is generally attributed to alcohol, has been commonly observed in children and other non-alcoholics. The evidence thus indicates that alcohol cannot seriously be regarded as a specific cause of cirrhosis of the liver.

JOSEPH B. KIRSNER.

STRAUSS, A., GROSS, CAPT. J. AND KYMAN, LT.S. Congenital atresia of the common bile duct. Ann. Surg., 117: 723 (May) 1943.

Ladd performed his first successful operation for congenital atresia of the bile ducts in 1927. Various type of anomalies exist but only 2 types are amenable to surgery: those that have an hepatic duct but no cystic or common ducts and those that have normal gall bladders, cystic, and hepatic ducts but a common duct with blind end. A white female infant was born one month prematurely and soon thereafter became jaundiced. Supportive therapy was given but the jaundice persisted; acholic stools continued and the infant did not gain weight. Operation was performed on the 35th day of life and at laparotomy there was found a common duct with blind end as it passed behind the duodenum. Choledochoduodenostomy was performed over a 2 cm. long piece of No. 10 Fr. catheter. The catheter was passed in the stool one week after operation. The patient was discharged on the 25th postoperative day with very little jaundice and normal stools. The differential diagnosis in such cases is discussed and it is emphasized that such infants may not become jaundiced for a number of days, and that the stools may seem normal in color soon after birth and yet have no bile in them. This case is the seventh successful case reported of atresia of the bile ducts.

FRANK NEUWELT.

BROOKS, B., AND WEINSTEIN, A. Cyst of the ampulla of Vater. Ann. Surg., 117: 728 (May) 1943).

A 30 year old male patient was admitted to Vanderbilt Hospital because of repeated attacks of abdominal pain accompanied by nausea, vomiting and possible jaundice. The patient had had his gall bladder drained at the age of 15 for what seemed an attack of acute cholecystitis. The above symptoms had begun 4 years previously but despite medical care, diet, etc., the patient

had obtained no relief. Roentgenologic examination revealed dilatation of the duodenum and the proximal jejunum, but the unusual lesion found at operation was missed even though in retrospect evidences of it could be seen on the X-ray plates. At operation the gall bladder was found to be surrounded by adhesions. The first 2 feet of the jejunum showed marked hypertrophy and dilatations. Stomach and first portion of the duodenum were normal; about one inch beyond the pylorus the duodenum became markedly dilated so that its diameter was approximately the same as that of the stomach. A mass could be felt within which, upon being pressed, was partially emptied into the dilated jejunum. Upon incision of the duodenum, a large polypoid mass was delivered through the operative wound. This mass was attached to the posterior wall of the descending duodenum, and was covered with what appeared to be normal duodenal mucosa; at the apex of the tumor a slit was present from which golden bile could be expressed. Incision into the mass revealed a central cavity which also seemed lined with duodenal mucosa and two small openings into the central cavity were noted: one led into a normal common duct and the other followed the direction of the duct of Wirsung. The mass was resected, except for a circular area of mucosa about the two apertures, and the duodenum closed. The gall stones were then removed and a small drain placed in the fundus of the gall bladder. The patient made an uneventful recovery. The authors point out that the anomaly was really of the duodenal wall and not an acquired dilatation of the ampulla of Vater.

FRANK NEUWELT.

ANEMIAS

DELIKAT, E. Intolerance to liver extract in pernicious anaemia. Brit. Med. J., 4295: 539 (May) 1943.

Among 200 patients with pernicious anemia who were treated over a 15 year period, 14 were encountered who became intolerant to liver by parenteral injection. None of these patients gave an allergic history, but in all of them the symptoms of intolerance were those of allergic hypersensitivity. The reactions varied from slight local manifestation at the site of injection to severe constitutional reaction with urticaria, vomiting, and asthma. For some of the reactions ephedrine or adrenaline were needed. Once sensitization became established, it applied to all brands of liver and in some cases a change to oral administration was required. The phenomenon was regarded as anaphylactoid and due to sensitization to liver. Two methods were used for parenteral administration of liver to intolerant patients. Lasting desensitization can be achieved by a course of liver injection in increasing doses over several weeks, or the required dose may be given in small injections preferably spread over a 2-day period.

HENRY TUMEN.

ULCER

TIMONEY, F. X. Perforated peptic ulcer. Ann. Surg., 117: 710 (May) 1943.

Perforated peptic ulcer has been found to have about a 20 per cent mortality, in most papers on the subject, but since the advent of sulfonamide therapy the mortality has been reduced and fewer post-operative complications occur. A consecutive series of 254 cases were studied; diagnosis was correct in 238 out of a total of 248 cases, either operated upon or proven by autopsy. One hundred twenty-six cases were described as perforated gastric ulcers, 116 as duodenal ulcers, and 2 as marginal ulcers. The disease is seen almost predominately in males, only 8 cases of perforation occurring in females. Roentgenologic examination for air under the diaphragm was done in 176 cases, and only in 93 of these was air demonstrated. The author emphasizes that in case any delay in operation is entailed by such examination it should be dispensed with since the diagnosis can be made on clinical grounds; furthermore air is demonstrated under the diaphragm in only a little over 50 per cent of cases. The author had a mortality of 19.5 per cent previous to the advent of chemotherapy; in a series of 49 cases in which sulfanilamide was implanted in the peritoneal cavity, the operative mortality was reduced to 4 per cent. The use of chemotherapy reduced the incidence of wound infections from 25.6 to 8 per cent.

The preoperative use of Wangensteen suction is emphasized as another cause for the reduced mortality in the more recent cases.

FRANK NEUWELT.

HOLLANDER, F., AND MAGE, S. A statistical method for evaluating the results of treatment for peptic ulcer. Surg. Gyn. Obs., 76: 533 (May) 1943.

There is widespread disagreement as to the relative merits of the various methods of treating peptic ulcer. Certain cure is not yet known, and recurrences are common. In the past, statistics on this matter have been inadequate and unreliable. A more effective method of tabulating and analyzing such statistics is laid out in this article. In order to cope with the problem of unfollowed cases, it was decided to accept the premise that the number of failures in a group of unfollowed patients is no more and may be less than the number of failures found in groups which were actually followed. Maximum and minimum estimates of the cumulative trend curve (by years) for the percentage incidence of post-therapeutic recurrence of ulceration are given by the new method. It is estimated that the average total incidence of recurrence following subtotal gastrectomy for duodenal ulcer is about 9 per cent. The basis of "statistical methodology" is discussed. Unless the importance of "statistical methodology" is recognized, statistics gathered in the future will have no more meaning than those taken in the past.

FRANCIS D. MURPHY.

PROCTOLOGY

BOLEN, H. L. Spasmodic rectal pain. New Engl. J. Med., 228: 564 (May) 1943.

Spasmodic pain in the rectum (proctalgia fugax) which is localized a short distance above the sphincter ani, has received scant attention in the literature. It appears without warning, is slightly gnawing at first, but increases steadily in intensity to a point that may cause loss of consciousness, then slowly disappears, leaving no ill effects except a sense of fatigue. The average attack lasts for about 15 minutes. The patient has a sensation of uneasiness at the anus, with a tightening sensation at the anal canal. A continuous dull ache is felt in the rectum, as though it were ballooning out. This neuralgic type of pain is not related to the intake of food, the type of food ingested, nor bowel function. It is about twice as common in men as in women. The attacks of proctalgia fugax are different from the crises of tabes dorsalis, from the nervous type of rectal pain called enteralgia or neuralgia of the mesenteric plexus, and from that of coccygodynia. A cardinal reason for establishing the correct diagnosis in these cases is the need for reassuring these patients that they do not have cancer of the rectum. The etiology of this condition is not known. A case of spasmodic rectal pain is reported in a 60 year old man. Sigmoidoscopic examination during an attack disclosed a rectal mucosa redder than normal. The mucosa seemed swollen and the vessels were prominent. The middle valve of Houston was more rounded than normal. With the passage of a considerable amount of gas, the patient noted relief of the pain. Sigmoidoscopic examination a week later revealed a normal rectum.

JOSEPH B. KIRSNER.

LIEBERMAN, W. Proctoscopic removal of rectal and sigmoid polyps with a technic of ligation. Rev. Gastroenterol., 10: 162 (May–June) 1943.

Because benign polyps of the rectum and sigmoid are precancerous their early removal and follow-up is very urgent. The author's technic of ligating the pedicle of a high polyp makes use of an ordinary snare, long enough to reach the growth through the appropriate proctosigmoidoscope, and a "friction slip-knot." Ligation is desirable as an additional safety measure preliminary to fulguration or snaring, in order to decrease the possibility of immediate or delayed hemorrhage. In addition to ligation all other precautions should be observed including post operative endoscopy and control of even minute bleeding. Descriptive diagrams of the "friction slip-knot" and snare accompany the report.

MICHAEL W. SHUTKIN.

SURGERY

LAUFMAN, H., AND BETTMAN, R. B. One-stage radical resection of the rectum by modified Lloyd-Davies technic. Am. J. Surg., 60: 243 (May) 1943.

Though the Miles technique for one-stage radical resection of the rectum and rectosigmoid has been exposed to variation and refinement, yet it has been most widely accepted and employed throughout the world. Because of certain shortcomings (especially in short, stocky, male patients with a short mesosigmoid) a simultaneous one-stage perineo-abdominal resection of the O. U., Lloyd-Davies type with the authors' modification, is recommended for more popular use. This simultaneous resection combines the advantages of the Miles abdomino-perineal resection with those of the Gabriel perineo-abdominal technique, without appreciably carrying over the disadvantages of either procedure. The recommended technique here fully described permits closing the pelvic peritoneum over an empty pelvis, accurate dissection, lithotomy-Trendelenberg position, clear vision and greater speed. Though 2 experienced surgeons synchronize their efforts in this method, one surgeon and 2 assistants may successfully complete the operation.

MICHAEL W. SHUTKIN.

ALLEN, A. W. The importance of the antral mucosa in the surgical treatment of duodenal ulcer. Southern Med. J., 36: 368 (May) 1943.

Approximately 80 per cent of patients with duodenal ulcer are satisfactorily treated by medical measures. Surgical interference is required in the remaining 20 per cent which comprises patients with acute perforation, obstruction resulting from cicatricial stenosis, and individuals over the age of 45 with massive hemorrhage. In addition to the above types of duodenal lesions requiring surgical intervention, there is a small group of cases classified as "intractable ulcers." It is now apparent that the previous surgical management of these patients by such conservative operations as pyloroplasty, gastroenterostomy, or gastroduodenostomy has not proved satisfactory. Radical subtotal gastrectomy, on the other hand, has yielded excellent results. According to Allen, the keynote of success in gastrectomy for duodenal ulcer lies in the entire elimination of the antral mucosa. Thus anastomotic ulcer developed in 5 of 9 patients treated by the Finsterer exclusion operation without removal of the mucosa of the antral segment. Three of these patients subsequently permitted additional surgery and were relieved by the elimination of the antral segment and the new ulcer area. In two individuals operated upon elsewhere, the anastomotic ulcer was similarly treated successfully. The antral segment has been denuded of its mucosa in approximately 20 additional cases as an adjunct to subtotal resection for exclusion. So far none of these patients has developed anastomotic ulcer; in fact they have done as well as those having a complete subtotal gastric resection. The excellent results in these patients are attributable to the elimination or marked reduction in acid secretion induced by the complete removal of the antral mucosal cells.

JOSEPH B. KIRSNER

CASTLETON, K. B. Biliary tract surgery. Am. J. Surg., 60: 190 (May) 1943.

This report represents the analysis of 411 biliary tract operations upon 401 patients by 77 different surgeons in 4 general hospitals. The average age for the group was 48.2 years while the ratio of female to male was 3 to 1. Gall stones were found in 288 of the 411 patients operated upon. A pathological study revealed 89 patients with acute cholecystitis, of which 12 died, and 313 with chronic and subacute cholecystitis. There were, in addition, 3 cases of carcinoma of the gallbladder, 2 of papilloma, and one carcinoma of the liver. The type of operation included 301 cholecystectomies, 61 cholecystostomies, 33 cholecystectomies with choledochostomy, 5 cholecystostomies with choledochostomy, 2 choledochostomies, 3 plastic operations, one cholecystduodenostomy, one cholecystgastrostomy, and 4 explorations with lysis of adhesions. The indications for common duct exploration are: (1) presence of palpable stones, (2) dilated common duct, (3) history of jaun-

dice. In this series the common duct was opened in 40 cases with a mortality of 15 per cent. The mortality rate for the entire group was 7.2 per cent per patient and 7.05 per cent per operation.

MICHAEL W. SHUTKIN.

TOTTEN, H. P. Simplified aseptic gastrojejunal anastomosis using the Rankin clamp. Am. J. Surg., 60: 227 (May) 1943.

The restoration of gastrointestinal continuity following gastric resection is the principal consideration. The method of closed anastomosis with crushing clamps is superior to the open method because of greater asepsis and hemostasis in the former. For this purpose as well as for perpetuating the proper gastroenteric continuity, the Rankin clamp is very well adapted. The complete surgical technique for subtotal gastrectomy, in which both the Rankin and Payr clamps are employed, is fully described.

MICHAEL W. SHUTKIN.

PATHOLOGY

KIRBY, A. H. M. Attempts to induce stomach tumors. I. The effect of cholesterol heated to 300°C. Cancer Res. 3: 519 (Aug.) 1943.

Numerous agents have been shown to induce a variety of benign and malignant tumors in the forestomach of rodents. In contrast, no well authenticated case of artificially induced adenocarcinoma of the glandular stomach of these animals had been reported until recently, when Stewart and Lorenz produced this lesion by local injection of methylcholanthrene. Roffo stated that he was able to induce adenocarcinoma and sarcoma in the glandular stomach of rats by feeding fats or cholesterol heated to 300°C, but this was not confirmed by Beck and Peacock. These authors were unable to obtain any glandular tumors with the feeding of overheated fats or oils.

Kirby reinvestigated the report of Roffo and particularly the statement that the oxidation of cholesterol is responsible for the presumed carcinogenic change induced in fats and oils by overheating. Rats were put on a basal diet which excluded any dietary deficiency. Cholesterol heated to about 300°C was fed to one group of these animals, and controls were fed the same amount of unheated cholesterol. No malignant growth was observed in any part of any rat. The only lesions seen were hemorrhagic erosions in the glandular stomach of those rats who died from starvation and cachexia caused by lung abscesses. Experimental and control animals were afflicted likewise in this respect. The author explains the results of Roffo by a multiple deficiency in the diets of the latter's animals. Thus, a deficient diet may really be necessary to uncover pathogenic properties in the agents under investigation. Finally, the chemistry of the pyrolytic products resulting from the overheating of cholesterol is discussed.

MANFRED HESS.

METABOLISM AND NUTRITION

SHARPLESS, G. R. Diet and epithelial hyperplasia in the forestomach of rats and mice. Cancer Res., 3: 108 (Feb.) 1943.

The author studied the effect of 2 types of deficiency diet (low protein and white flour) on the epithelium of the forestomach of rats and mice. With great regularity lesions of ulceropapillomatous character appeared on the mucosa of the forestomach, sometimes covering practically the entire mucosa. The blastogenic effect of the low protein diet could be abolished by addition of cystine or caseine, and no lesions appeared during white flour feeding if riboflavin, cystine, nicotinic acid or rice polishings concentrate were added to this diet. Pepsin, hydrochloric acid, and sodium taurocholate showed an enhancing effect on the lesions. Control studies excluded the possibility that the lesions might be a result of starvation. The action of the protective factors seems to be interdependent, so that a deficiency of one of them may prevent the effective action of others.

MANFRED HESS.

HOGAN, A. G., AND PARROTT, E. M. Isolation of the antianemia factor (vitamin Bc) in crystalline form from liver. Science, 97: 404 (Apr.) 1943.

Under certain dietary conditions chicks fail to grow and they develop a severe anemia which can be cured with liver extracts.

The responsible factor, a member of the B complex, has been concentrated about 60-fold in a crude liver extract. This article reports the preparation of the compound in pure form. Some of the chemical and physical characteristics of the substance are given. The identity of Hogan's anti-anemic factor and Peterson's "eluate factor" is established. It is probable that these factors are identical with Williams' "folic acid" factor. The present authors designate their substance as Bc.

IRA MANVILLE.

BLOOMFIELD, A. L., AND LEW, W. Increased resistance to ulcerative cecitis of rats on a diet deficient in the vitamin B complex. J. Nutrit., 25: 427 (May) 1943.

Among rats of a strain developing a high incidence of infectious inflammation of the cecum after 3 months of age, those which received a diet deficient in the vitamin B complex over a period of months failed to develop "spontaneous ulcerative cecitis" except, very mildly, in an occasional animal. One-half of the litter-mate controls, on the other hand, had the disease, for the most part in well-advanced form. This, then, is an example of increased resistance to infection, rather than increased susceptibility, brought about by undernutrition and vitamin deficiency.

ARTHUR E. MEYER.

SULLIVAN, R. A., BLOOM, E., AND JARMOL, J. The value of dairy products in nutrition. J. Nutrit., 25: 463 (May) 1943.

Twelve different types of cheese have been analyzed for riboflavin, pantothenic acid, nicotinic acid, and biotin. Only minor variations were observed in the concentrations of riboflavin, but the other factors appeared to be quite dependent upon the age of the cheese and the ripening process by which the cheese was produced.

ARTHUR E. MEYER.

PHARMACOLOGY

LEROY, W., AND COLE, W. H. The intraperitoneal administration of sulfadiazine. Surg. Gyn. Obs., 76: 524 (May) 1943.

The value of sulfadiazine in comparison with sulfanilamide for intraperitoneal administration is discussed. Sulfadiazine crystals were implanted in the peritoneal cavities and wounds of 68 patients operated on for lesions which, in many cases, resulted in contamination of the peritoneum. The effect of sulfanilamide was studied on 62 patients. Wound infections occurred in 4.04 per cent with sulfadiazine and 14.05 per cent with sulfanilamide, indicating that sulfadiazine was superior to sulfanilamide in prevention of wound infection. No toxicity was noted with sulfadiazine; there was 1 wound disruption and 1 fatality from peritonitis, but these were felt to be unrelated to the use of sulfadiazine. Six grams was thought the best routine dose: 4 gm. implanted in the peritoneal cavity and 2 grams in the peritoneal wound at the end of the operation. The sulfonamides should be sprinkled evenly over the wound. The blood level following sulfadiazine was more persistent than that following sulfanilamide, and 5 g. of sulfadiazine intraperitoneally resulted in higher blood levels than the same dosage of sulfanilamide. If sulfonamide action is desirable for a few days after operation 3 g. of sodium sulfadiazine may be given twice daily intravenously. The authors are of the opinion that sulfadiazine is safer and more effective than sulfanilamide.

FRANCIS D. MURPHY.

MISCELLANEOUS

ROBINSON, C. S., LUCKEY, H., AND MILLS, H. Factors affecting the hydrogen ion concentration of the contents of the small intestine. J. Biol. Chem., 147: 175 (Jan.) 1943.

It has been demonstrated in several species of animals that the entire intestine adjusts the reaction of its contents to fit a definite pattern. This report deals with the acid-base alteration by which this adjustment is accomplished in dogs. The changes during the adjustment of higher or lower initial values to those characteristic of the portion of the gut involved were followed by observing average values for pH, bicarbonate, and CO_2 tension in a number of loops in various sections of the intestines. Also, the effects of ammonium chloride acidosis and sodium bicarbonate alkalosis were

studied. Observations on humans were made by the Miller-Abbott intubation technique.

The results indicate that the increase in pH in the jejunum is due to a combined decrease in CO_2 tension and increase in bicarbonate. In the ileum, the picture abruptly changes and ileal loops show high values due to increased bicarbonate. When alkaline solutions are introduced into loops, the pH is promptly reduced to acid levels due to a relatively rapid influx of CO_2. Subsequent additions of bicarbonate return the values to the equilibrium point. Ammonium chloride acidosis causes no significant change in the pH and hence does not increase calcium absorption by increasing the acidity in the gut. Bicarbonate alkalosis produces a rise in pH. The reaction of the human jejunum is the same as that of the dog.

IRA A. MANVILLE.

ABELS, J. C., PACK, C. T., AND RHOADS, C. P. Metabolic studies in patients with cancer of the gastrointestinal tract. XVII. The conjugation of phenols. Cancer Res., 3: 177 (Mar.) 1943.

Signs of hepatic dysfunction were found rather frequently in patients with gastrointestinal cancer. Nearly all the livers of a group of patients suffering from stomach cancer showed fatty infiltration and a decrease in glycogen content; also, 90 per cent of this group eliminated abnormally small amounts of glucuronates in the urine. In the present study the authors examined the urinary excretion of conjugated phenols in the hope that they might find a clue regarding both hepatic dysfunction and the deviation of glucuronate excretion.

A group of 12 normal persons showed a daily average elimination of total phenol of 461.5 mg., of which the conjugated phenol constituted 31.4 per cent. The average daily glucuronate elimination was 462.2 mg. A group of 5 patients with hepatic cirrhosis showed the following: total phenol 516.4 mg., of which only 15.2 per cent was conjugated; daily glucuronate elimination 153.4 mg. In a group of 12 patients with gastrointestinal cancer, the total phenol output and the conjugated phenol fraction showed normal values. Glucuronate elimination, on the other hand, was low (207.2 mg. daily). Total phenol output depends chiefly on the composition of the diet and cannot be considered to have any essential significance in the cases studied. Esterification of phenols occurs mainly in the liver. The livers of the cancer patients under investigation retained their faculty of carrying out this function though the synthesis of glucuronic acid seemed to be impaired. Cirrhotic livers, on the other hand, showed considerable impairment of their ability to conjugate phenols.

MANFRED HESS.

REHM, W. S. Electrical energy output of the resting stomach as determined by shunting its potential. Am. J. Physiol., 139: 1 (May) 1943.

The potential of the "resting" body of the dog's stomach was shunted through electrodes which had a resistance of approximately the same order of magnitude as the stomach. Currents of 67.8 to 276 microamperes per square centimeter could be drawn off continuously. Evidence is presented that there is no maintained depolarization of the potential upon the withdrawal of currents of the above magnitudes.

ARTHUR E. MEYER.

WARKENTIN, J., WARKENTIN, L., AND IVY, A. C. The effect of experimental thyroid abnormalities on appetite. Am. J. Physiol., 139: 139 (May) 1943.

Selective feeding, using relatively pure constituents, will support good health and growth in most rats for a period of over one year. The diet selected by rats varies according to age; the critical age dividing "young" and "old" rats is about 4 months. Older rats eat less food per 100 gm. body weight than do young rats. Young rats select more fat and salt than do older rats, while the latter eat more protein. However, all groups ate much more protein than is allowed in the Osborne and Mendel diet. The alternate intake of fat and carbohydrate is so definite in some rats as to suggest that they "eat for calories." Six rats were made hypothyroid, 6 others were made hyperthyroid, and 6 were kept as normal controls. The thyroidectomized rats showed

a markedly greater decrease in food intake than did the normals, while the hyperthyroid rats ate much more food than either of the other 2 groups. No characteristic qualitative differences in food selection were noted due to thyroid abnormalities.

ARTHUR E. MEYER.

JONES, C. M. Alimentary-tract disturbances secondary to emotional or physical trauma. New Engl. J. Med., 228: 612 (May) 1943.

The author comprehensively reviews the various types of digestive disturbances resulting from emotional and physical traumata associated with war conditions. Particular attention is directed to the striking incidence of gastro-intestinal complaints in military hospitals. Practically all reports indicate that the vast majority of men in military service complaining of gastro-intestinal symptoms had such symptoms prior to induction into service. It is agreed that the most significant factors contributing to the recurrence of distress are lack of a suitable diet and psychologic disturbances incident to military service. A marked increase in the incidence of digestive disturbances, including perforations of peptic ulcers, had been noticed also in the civilian English population. Additional topics discussed in this article include acute ulcers of the stomach and duodenum following extensive burns and direct injury to the gastro-intestinal tract by the ingestion of irritating substances or of foreign bodies and by the trauma incident to endoscopic examination for diagnostic purposes. Of equally great significance are the indirect injuries to the gastro-intestinal tract resulting from nonpenetrating trauma. These may occur as a result of a crushing injury in which an external force compresses the bowel against the spine or pelvic bones, a tearing injury that may result from a violent force applied at a tangent to the body, and severe bruising injuries that increase the normal pull on an organ. Distention of the intestine with food or fluid frequently contributes to the likelihood of rupture following a blow from a blunt object. Peptic ulcers secondary to trauma apparently do occur, although it may be difficult to establish conclusively the relationship from a medico-legal standpoint. Traumatic appendicitis appears to be extremely rare. Of great interest at present are the concussion injuries to the gastro-intestinal tract resulting from blasting or bombing. Any portion of the digestive tract may exhibit pathologic changes consisting of hemorrhage, varying from punctiform spots under the serosa to large annular extravastrions, and occasional rupture of the bowel.

JOSEPH B. KIRSNER.

ALWAYS A *QUALITY* TRADE-MARK

Recent Products of STRASENBURGH *Research*

★ **MAXITATE**
The stabilized preparation of Mannitol Hexanitrate.

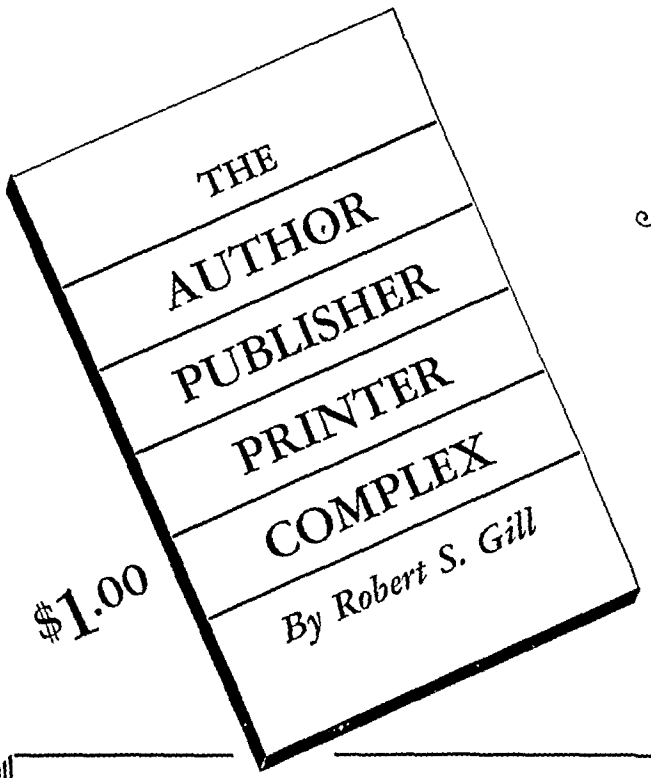
★ **METROPINE**
(Methyl Atropine Nitrate, Strasenburgh.) A safe, reliable spasmolytic, less toxic and of lesser mydriatic action than Atropine.

★ **ALOPECTOSE**
A reliable preparation for the treatment of intestinal dysfunctions, infectious diarrhoeas and peptic ulcers.

Since 1886, the R. J. Strasenburgh Company has devoted its efforts to being of real service to the American medical profession. To forward these efforts it has constantly maintained rigid control of quality and has promoted a modern research program in the development of new products.

Today in the Strasenburgh research laboratories, scientists are pioneering the development of outstanding products to meet today's medical requirements. Strasenburgh formulae always come to you fully tested, completely dependable.

R. J. STRASENBURGH Co.
PHARMACEUTICAL CHEMISTS SINCE 1886
ROCHESTER, NEW YORK



A book for authors; it will save energy, worry, and CASH.

Condensed into 80 pages, there is consideration of the important preliminaries by which the manuscript is pulled into shape—a state the publisher harmlessly calls fair copy.

There are sensible explanations and reasons why of the "lyrics of a book publishing agreement."

IT TELLS what a manuscript must be like "typescriptically" and how to mark it in preparation for transmutation into type.

Why copy prepared not in accord with requirement is likely to cost the author money.

About royalty arrangements and related matters.

What original copy for illustrations has to be like.

How to cast out "verbal bums."

What the separate functions of author, publisher, and printer are—and of the hundred-and-one details that make the relationship profitable and pleasant.

ANOTHER BOOK FOR THE WRITER AND EDITOR

Preparation of Scientific and Technical Papers

By SAM F. TRELEASE, *Columbia University and* EMMA SAREPTA YULE

Real help in every stage of preparation. "Its excellence lies in the careful discussion of the organization of material and the mechanics of expository writing."

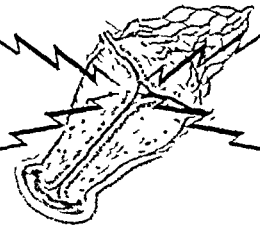
The concise text sets forth certain standards which, if author and publisher both refer to them, will eliminate much useless friction.

The book not only makes your task of writing easier, but enables you to get your material into the printed dress in which you desire to see it.

Third edition, revised and enlarged, 117 pages. $1.50

THE WILLIAMS & WILKINS COMPANY, BALTIMORE, MD.

Attacks Spasm from 2 angles:



1 MUSCULOTROPIC
—local action upon muscle

2 NEUROTROPIC
—through nerve supply to smooth muscle

—thus providing relief whether spasm is of muscular or neural origin

PAVATRINE

This potent, safe, non-narcotic antispasmodic is a recent result of intensive research in the Searle laboratories.

In dysmenorrhea, gastrointestinal and urinary bladder spasm—PAVATRINE has shown high spasmolytic potency, ability to abolish uterine contractions, increased safety.

While Pavatrine is non-narcotic, its action in dysmenorrhea has been described as *morphine-like.*

Literature showing the smooth muscle relaxing action of Pavatrine, together with dosage and administration, is available. Please address your request to the Searle Medical Dept., P.O. Box 5110—B, Chicago 80, Illinois.

Pavatrine is supplied in bottles of 20, 100 and 1000 s.c. tablets of 2 grs. each.

G·D·SEARLE & CO.
ETHICAL PHARMACEUTICALS SINCE 1888
CHICAGO
New York Kansas City San Francisco

Pavatrine is the registered trademark of G D Searle & Co.

SEARLE
RESEARCH IN THE SERVICE OF MEDICINE

Consolidating clinical experience and laboratory research

ALLERGY, ANAPHYLAXIS AND IMMUNOTHERAPY

Basic Principles and Practice

By **BRET RATNER, M.D.,** *Clinical Professor of Pediatrics, New York University College of Medicine; Visiting Pediatrician and Director of Pediatrics, Sea View Hospital; Associate Attending Children's Medical Service, Bellevue Hospital; Consultant Pediatrician, French Hospital.*

Physicians and investigators have waited for a book like this. It spans the wide gaps existing in the texts on allergy, bacteriology, immunity and therapy.

In the new volume you find all the basic principles of allergy, anaphylaxis, shock and present-day immunotherapy which includes such diversified subjects as prophylaxis and treatment of the infectious diseases, sulfonamide therapy, transfusions, blood substitutes, and convalescent sera.

Dr. Ratner proceeds from description of the materials, methods of their preparation, and modes of administration to the details of immunotherapy in more than forty infectious diseases, among them gonoccocal infections, meningitis, anthrax, pneumonia.

The second part of the book centers on serum allergy and serum sickness and encompasses the principles of allergy in general.

A unique feature is the graphic exposition of the allergic state in a series of 86 illustrations presented moving-picture-like. The sequence progresses from sensitization and shock reactions of animals all the way to scratch tests and parenteral desensitization in human allergy.

850 pages, 174 illustrations **$8.50**

The Williams & Wilkins Company
Baltimore-2, Md.

The research worker will value particularly the discussion of such subjects as:

1. Anatomy and physiology of the minute vessels of the skin.
2. Leukopenia and eosinophilia —covered more extensively than in most texts on blood cytology.
3. The R H factor in the blood and iso-immunization.
4. The chemistry and nature of serum and serum proteins.
5. The nature and formation of antibodies, antisera, toxins, and toxoids.
6. The nature of homologous blood and blood substitutes.
7. The chemistry, pharmacology and mode of action of sulfonamides.
8. Duran-Raynal's spreading factor.
9. Relation of human and animal anaphylaxis to general shock.
10. Surgical shock and its dynamics.
11. The alarm reaction and counter shock phenomena.
12. The histamine concept of anaphylaxis.
13. The arteriolar spasm theory of wheal formation.
14. Allergy of the central nervous system.
15. Allergy to sulfonamide therapy and its underlying mechanism.
16. Allergy to transfusions.
17. Physiological pathology of the allergic state.
18. The blood chemistry of shock.

The clinical parts of the book keep the investigator in touch with the needs of the practicing physician and show him where further investigation is needed.

The comprehensive bibliography and the carefully prepared index add greatly to the usefulness of the book.

PHARYNGEAL DISTRESS

NUPORALS* . . . the nonnarcotic . . . local anesthetic . . . pleasant tasting lozenges . . . find wide usefulness in ameliorating pharyngeal distress associated with

- ▶ Passage of stomach tube
- ▶ Pharyngeal examination
- ▶ Bronchoscopic examination
- ▶ Gastroscopic examination

As well as in alleviating discomfort of sore throats.

★

NUPORALS

contain 1 mg. Nupercaine*

*Trade Marks Reg U S Pat Off

★

Ciba

Tomorrow's Medicines from Today's Research

Pharmaceutical Products, Inc.

SUMMIT, NEW JERSEY

CANADIAN BRANCH · MONTREAL, QUEBEC

STEDMAN'S

Practical

Medical Dictionary

15th Edition

This time you can look forward to more than an ordinary revision of the famous dictionary. The entire work was reset for the new edition.

Therefore an unusual number of additions, eliminations, corrections could be made without regard to the cost of such changes.

Basically the dictionary retains the features that have made STEDMAN irreplaceable on the desk of physicians and thousands of others who need a complete dictionary that is authoritative, reliable and easy to use.

It includes all the medical, surgical, pharmacal, biological, chemical, dental and thousands of other related scientific terms that you encounter daily; and it succeeds, by clear definitions and plain instructions about pronunciation, in making every word easily your own.

Noteworthy revisions include

the section on vitamins

the biochemical and chemotherapeutic compounds

terms in the fields of allergy and hematology (entirely rewritten)

the terminology of the bacteria

Special features:

Greek roots given in Roman letters

Introductory Section on Medical Etymology

Appendix covering Weights and Measures, Stethoscopic Abbreviations, Temperature and Barometer Scales, Chemical Elements, Pathogenic Microparasites, Anatomical Terms

The editor of the 15th edition is Dr. Stanley Thomas Garber who joined Dr. Stedman as a collaborator on the preceding edition. He shows in the new STEDMAN that he not only upholds the fine tradition built up during nearly thirty years but also knows how to modernize this indispensable reference book.

1272 double column pages, illustrated, and 23 plates
The price of the new Stedman Dictionary remains

$7.50

for the thumb-indexed copy, in semiflexible cover, gold stamped.

The Williams & Wilkins Company, *Baltimore-2, Md.*

A Threatened Attack...

Often Aborted by Taking

HORLICK'S MALTED MILK TABLETS

Peptic ulceration and pseudo ulcer appear definitely on the increase—due in great measure to high tension living in a world at war.

To help forestall the distressing symptom of hunger-pain associated with the ulcer diathesis, a noted authority* stresses the importance of an *immediate intake* of food *at time of attack*.

> "Because of the need for taking food quickly before the acid can cause much irritation of the gastric or duodenal mucosa, I advise the patients always to carry with them some *tablets of malted milk*. The minute pain is felt, or preferably some time before it is expected, half a dozen such tablets should be chewed up and swallowed, preferably with a little water.
>
> "If food is taken in this way, a threatened attack may be aborted, and the patient may be spared several days or weeks of discomfort."

*Alvarez, W. C.: "Nervousness, Indigestion and Pain," published by Paul B. Hoeber, Inc., pp 363-364.

HORLICK'S PLAIN
Powder or Tablets

HORLICK'S FORTIFIED
A, B_1, D & G Powder or Tablets

HORLICK'S

The *COMPLETE* Malted Milk—Not Just a Malt Flavoring for Milk

(In writing to advertisers, please mention the **journal**—it helps.)

CONSERVATION OF SCHOLARLY JOURNALS

The American Library Association created in 1941 the Committee on Aid to Libraries in War Areas, headed by John R. Russell, the Librarian of the University of Rochester. The Committee is faced with numerous serious problems and hopes that American scholars and scientists will be of considerable aid in the solution of one of these problems.

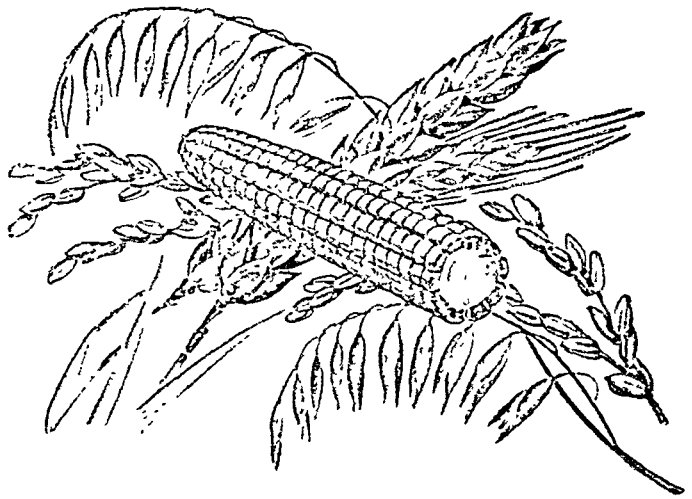
One of the most difficult tasks in library reconstruction after the first World War was that of completing foreign institutional sets of American scholarly, scientific, and technical periodicals. The attempt to avoid a duplication of that situation is now the concern of the Committee.

Many sets of journals will be broken by the financial inability of the institutions to renew subscriptions. As far as possible they will be completed from a stock of periodicals being purchased by the Committee. Many more will have been broken through mail difficulties and loss of shipments, while still other sets will have disappeared in the destruction of libraries. The size of the eventual demand is impossible to estimate, but requests received by the Committee already give evidence that it will be enormous.

With an imminent paper shortage attempts are being made to collect old periodicals for pulp. Fearing this possible reduction in the already limited supply of scholarly and scientific journals, the Committee hopes to enlist the cooperation of subscribers to this journal in preventing the sacrifice of this type of material to the pulp demand. It is scarcely necessary to mention the appreciation of foreign institutions and scholars for this activity.

Questions concerning the project or concerning the Committee's interest in particular periodicals should be directed to Dorothy J. Comins, Executive Assistant to the Committee on Aid to Libraries in War Areas, Library of Congress Annex, Study 251, Washington, 25, D. C.

(In writing to advertisers, please mention the journal—it helps.)



In Gastrointestinal Affections

When a bland diet is called for, cereal breakfast foods (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron) make a noteworthy contribution to nutritional needs and present many advantages.

Cereals, such as corn flakes, corn cereals, farina, oat cereals, oatmeal, puffed cereals, rice cereals, wheat cereals, wheat flakes, are mechanically as well as chemically bland. They evoke no undue amount of acid gastric secretion, hence cause no discomfort. They are digested with ease and, since their fiber content is notably low (an average of 1.3%), virtually in toto.

Frequently they present an excellent means to make milk acceptable to the patient.

Because of the wide variety of form and taste in which they are available, cereals can be given several times daily, without jading the appetite. Each such feeding of 1 oz. of cereal (prepared or to be cooked), 4 oz. of whole milk, and 1 teaspoonful of sugar, presents the following (composite average) nutritional values:

Calories	205
Protein	7.0 Gm.
Carbohydrate	33.0 Gm.
Fat	5.0 Gm.
Thiamine	0.18 mg.
Riboflavin	0.30 mg.
Niacin	0.84 mg.
Calcium	0.16 Gm.
Iron	1.29 mg.

Bland diets have long presented a problem in their deficiency of certain essential nutrients. When cereals are made an integral part of such a diet, this difficulty is considerably lessened.

The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

CEREAL INSTITUTE, INC.
135 SOUTH LA SALLE STREET • CHICAGO 3

A cooperative effort to present the nutritional value of cereal breakfast foods (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), undertaken jointly by THE CREAM OF WHEAT CORP.... GENERAL FOODS CORP.... GENERAL MILLS, INC.... KELLOGG COMPANY .. NATIONAL BISCUIT COMPANY ... FILLSBURY FLOUR MILLS COMPANY ... THE QUAKER OATS COMPANY ... CAMPBELL CEREAL CO. .. ALBERS MILLING CO.

(In writing to advertisers, please mention the journal—it helps.)

PRINCIPLES & PRACTICE OF AVIATION MEDICINE • *Shows your task in a nation taking to the air*

By HARRY G. ARMSTRONG, M.D.

Capt. Med. Corps, U. S. Army, Director, The Aero Medical Research Laboratory, Wright Field

"Constitutes an epoch in this field. . . . Here is the *one* book which makes available to the physician advice necessary to examine pilots, to inform patients about flying and to take care of many of the illnesses and emergencies associated with modern aviation."—*Journal of the A. M. A.*

It coordinates for the first time the advances in medical, physiological, and psychological understanding that have been made in a decade of immense development of aviation. Mechanical details are brought in just enough to emphasize their physical and medical applications. Here are in addition to many original contributions of the author, based on a tremendous personal experience, the essential results of more than 4000 separate papers on the subject. The book is required reading for flight surgeons and medical examiners, ascinating for every physician.

608 pages, 86 figures, $6.50

THE WILLIAMS & WILKINS COMPANY, BALTIMORE, MD

This book won $1,000

Biography of the Unborn

By MARGARET SHEA GILBERT

"Without doubt the finest exposition of man's first nine months—told without loss of dignity. Brings an air of excitement and enthusiasm into the high adventure of being born"—*Harry Hansen, in New York World Telegram.*

Illustrated, 142 pages, $1.75

The Williams & Wilkins Company, Baltimore

SEX AND INTERNAL SECRETIONS

SECOND EDITION

EDGAR ALLEN, Editor

"No book exists in any language to challenge the supremacy of this work in authoritativeness or comprehensiveness."—*Surgery, Gynecology and Obstetrics.*

1370 pages, 454 illustrations, $12.00

THE WILLIAMS & WILKINS COMPANY

BALTIMORE, MARYLAND

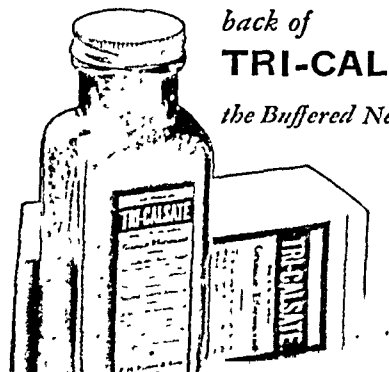
15 YEARS

OF CLINICAL EXPERIENCE

back of

TRI-CALSATE

the Buffered Neutral Antacid



. . . this is indeed proof of its efficacy. In the treatment of hyperchlorhydria, heartburn, gastric and duodenal ulcers, maximum (Sippy) dosage of TRI-CALSATE can be maintained without harmful systemic effects. Available on Rx in 4½ oz. and 1⅛ oz. bottles

Write for trial package and literature.

F. H. PAXTON & SONS, INC.

460 S. Ohio St. Manufacturing Pharmaceutical Chemists Chicago, Ill.

Sleep?..

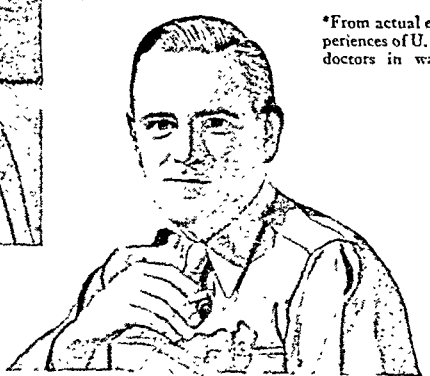
WHAT'S THAT?

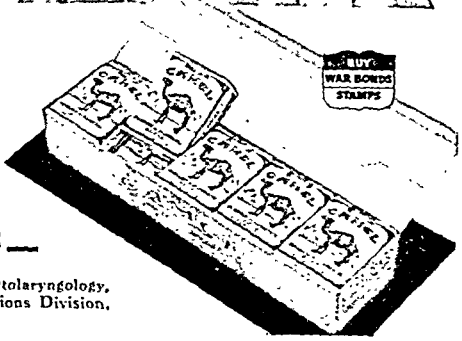
Now—a delicate brain job . . . then another . . . and another . . . to the tune of mortar fire . . . blast . . . shock! Steady . . . steady—easy now. "O. K. . . . clear the table! Next!" Operating . . . treating . . . night and day . . . Two hours sleep in seventy-two! . . .*

Yet that's just a side glance into a war doctor's life. When does he relax? Seldom, but that's when he's eager for a cheering smoke. Camel his likely choice—the fighting man's favorite**—for mildness, sheer good taste.

Friends, relatives in service? Remember them often—with a carton of Camels—the gift of gifts for service men!

*From actual experiences of U. S. doctors in war.





1st in the Service

**With men in the Army, Navy, Marine Corps, and Coast Guard, the favorite cigarette is Camel. (Based on actual sales records.)

Camel

costlier tobaccos—

New reprint available on cigarette research—Archives of Otolaryngology, March, 1943, pp. 404-410. Camel Cigarettes, Medical Relations Division, One Pershing Square, New York 17, N. Y.

GASTROENTEROLOGY

Owned by and Official Publication of the
American Gastroenterological Association, Inc.

Issued monthly, two volumes a year. Subscription price $3.00 per volume. For countries outside the Postal Union, add 25 cents a volume. Subscriptions of members of the Association are included in membership dues and are handled by the Association. Send other subscriptions to the publishers or agents listed below.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of that volume be out of print when subscription is received, the pro-rata value will be credited to the next volume, and renewal invoice adjusted accordingly.

Subscriptions should be renewed promptly. The publishers cannot guarantee to supply back issues on belated renewals.

Claims for copies lost in the mails must be received within 30 days (domestic). Changes of address must be received within two weeks of the date of issue. For the duration of the war, delivery overseas is at the subscriber's risk.

Correspondence concerning business matters should be addressed to the publishers.

INSTRUCTIONS TO AUTHORS

GASTROENTEROLOGY invites clinical and investigative contributions of interest to general practitioners as well as to specialists, which deal with the diseases of digestion and nutrition, including physiological, biochemical, pathological, parasitological, radiological and surgical aspects. Reviews, editorials, abstracts, and book reviews will be provided by the Editorial Board.

Submission of a paper implies that it will not be published elsewhere. Papers will be published within 3 or 4 months after receipt, in order of their receipt, except when revision is required.

Address manuscripts and correspondence pertaining thereto to:

DR. W. C. ALVAREZ, *Editor*
Mayo Clinic
Rochester, Minnesota

DR. A. C. IVY, *Assistant Editor*
303 E. Chicago Ave.
Chicago, Ill.

Manuscripts should be carefully prepared according to the following instructions:

Typewritten copy, double-spaced with a 1.5 inch margin on the left. Tables, references, footnotes and figure-legends on separate sheets. Construct illustrations and tables with the page-size of the journal in mind, arranged to conserve vertical space. Glossy prints of photographs are preferable. Graphs on white board or blue-lined heavy paper, with lettering and guidelines in India ink. Illustrations that require retouching or redrawing not accepted unless expense is defrayed by the author. A reasonable amount of tables and illustrations is allowed without charge; important additional material may be allowed at cost to the author, at the discretion of the editor.

Number references serially in the text and list them at the end of the paper in the same order. They should conform to the Quarterly Cumulative Index Medicus: Author's name and initials, journal, volume (arabic), initial pages, and year. Omit title of article.

Journal is not responsible for loss of manuscript in the mail. Authors should retain a copy.

Galley proofs are sent to the author. Alterations in type or illustrations will be charged to the author if they exceed 10% of the cost of original composition.

Reprints will be furnished when ordered in advance. Their number will be limited only when such sale is prejudicial to the interest of the Journal. A table showing cost of reprints, with an order slip, is sent with proof.

AGENTS

For Australia: Angus & Robertson, Limited, 89-95 Castlereagh Street, Sydney.

For the British Empire, except Australia and Canada: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, WC. 2, London, England.

For Canada: Wm. Dawson & Sons, Ltd., 70 King Street East, Toronto.

THE WILLIAMS & WILKINS COMPANY

Publishers of Scientific Books and Periodicals

Mt. Royal and Guilford Aves., Baltimore-2, Md., U. S. A.

PUBLISHERS OF: *Medicine, Journal of Urology, Journal of P[illegible] and Experimental Therapeutics, American Journal of Tropical Medicine, Journal of Immunology, Journal of [illegible], Quarterly Review of Biology, Journal of Bacteriology, Chemical Reviews, Soil Science, Soci[illegible], Physiological Reviews, Chemistry, Occupational Therapy and Rehabilitation, The American Journ[illegible], Philosophy of Science, Medical Classics, Journal of Investigative Der[illegible], Medical Care, Psychosomatic Medicine, Gastroenterology.*

KONSYL

A Rational Regime in the Treatment of Constipation

The undesirable ingredients such as irritating drugs, coarse roughage, and mineral oils are not found in KONSYL. It is the original non-habit forming concentrated vegetable mucilloid made from Plantago Ovata, which prevents constipation by *absorbing water and swelling* into a soft, bland "jelly" bulk lubricating the bowels without irritation or leakage.

Write for clinical test samples and literature

Also manufacturers of L. A. FORMULA containing Vitamin B_1, Lactose, Dextrin and Plantago Ovata Concentrate.

Serving Physicians since 1885

BURTON, PARSONS & CO.
WASHINGTON, D. C.

Another Humphreys Weather Book

You enjoyed FOGS AND CLOUDS, WEATHER PROVERBS AND PARADOXES, RAIN-MAKING.

The new one is

WEATHER RAMBLES

By WM. J. HUMPHREYS

Longtime Meteorological Physicist, U. S. Weather Bureau

Twenty weather "adventures" about—for instance—the prairie twister; what the trees murmur about; the stuff called air; the structure of the atmosphere; where rain comes from; counting and weighing the air; what would happen if Greenland's ice should melt—as it *is* melting.

Cloth. 5½ x 8. 265 pp. 37 illustrations. $2.50

THE WILLIAMS & WILKINS COMPANY
Publishers of Scientific Books and Periodicals
Baltimore, Md., U. S. A.

Normal function of the biliary apparatus is indispensable in the process of digestion and absorption of food and vitamins. Disturbances involving bile secretion seriously affect function not only in the biliary tract, but also in the small intestine and colon with the resultant manifestations of constipation, bloating, post-prandial distress and epigastric pain—symptoms of stasis in the biliary tract.

EXICOL

(OLEIC ACID and BILE SALTS)

has proven a most gratifying adjunct in the treatment of such symptoms, whether caused by organic or functional disturbances in the biliary tract (1, 2, 3, 4).

EXICOL exerts a two-fold action on the biliary apparatus.

1 Stimulates gall bladder contraction evacuating concentrated bile into the intestine (Oleic Acid effect).

2 Increases the flow of bile from the liver (Bile Salts effect).

In this manner it helps to overcome stasis in the biliary tract also furnishing adequate amounts of bile to the intestinal tract to aid normal physiological processes. The pharmacologic action of EXICOL has been repeatedly demonstrated both in human and animal studies. (5, 6).

INDICATIONS: Chronic cholecystitis, chronic (non-calculous) cholangitis, functional biliary insufficiency and preoperative and post-operative management of biliary tract conditions.

DOSAGE: Two capsules t.i.d., a.c. Marketed in boxes of 36 and 100 capsules.

● LITERATURE ON REQUEST ●

1. Med. J. and Rec. 137:201, 1933
2. Clin. Med. and Surg. 40:78, 1933
3. J. A. M. A. 99:591, 1932
4. J. Lab. and Clin. Med. 18:1016, 1933
5. Am. J. Roentgenol. 19:341, 1928
6. J. Lab. and Clin. Med. 19:567, 1934

BROOKLYN SCIENTIFIC PRODUCTS CO., INC., 70 Fifth Avenue, New York 11, N.Y.

(In writing to advertisers, please mention the journal—it helps.)

ANAYODIN

BRAND OF CHINIOFON

CLINICALLY
PROVEN

EFFECTIVE
IN TREATMENT OF
AMEBIASIS

LITERATURE ON REQUEST

ERNST **BISCHOFF** COMPANY
INCORPORATED
Ivoryton Conn.

INDEX TO ADVERTISERS

Rx

Tablets **Barbidonna**
(Vanpelt & Brown) No L

Sig· One tablet before each meal and at bedtime

Martin MD

BARBIDONNA

TABLETS

The Modern ANTISPASMODIC and SEDATIVE

BARBIDONNA TABLETS are specially compounded to meet the exacting requirements of the medical profession. They are time tested and acclaimed eminently effective.

FORMULA
Each Tablet Contains
PHENOBARBITAL—¼ gr. BELLADONNA ALKALOIDS (hyoscyamine, atropine and scopolamine) equivalent approximately to 5 minims of Tr. Belladonna.

Supplied in Bottles of 100 and 500 Tablets

BARBIDONNA is a balanced blend of the principal belladonna alkaloids—hyoscyamine, atropine and scopolamine—with phenobarbital. Its properties exert central and peripheral actions—both of which contribute to the therapeutic results obtained.

—Samples and literature upon request.—

All products bearing the VANPELT & BROWN label are processed in our own plant and guarded for quality and uniformity by rigid laboratory control.

VANPELT & BROWN, Inc.

Manufacturing Pharmaceutical Chemists

RICHMOND VIRGINIA

IN DISORDERS OF GASTRIC FUNCTION

Gastron

REG. U.S. PAT. OFF.

GASTRON is an original extract of the organic and inorganic constituents of the entire mucosa of the hog-stomach, including the pylorus The acidified and aromatized extract is incorporated in an aqueous-glycerin-propylene glycol menstruum which preserves the enzymatic activity The preparation contains no alcohol. It is accurately standardized by assay.

GASTRON is indicated as replacement therapy in atrophic gastritis, and as an aid in the treatment of chronic gastritis. It is of value as adjunctive treatment in the anemias, and in certain gastric deficiencies associated with convalescence and old age It is worthy of trial in the nausea and vomiting of pregnancy.

GASTRON *WITH IRON* is available also for prescription use.

ORIGINATED AND MADE BY

FAIRCHILD BROS. & FOSTER

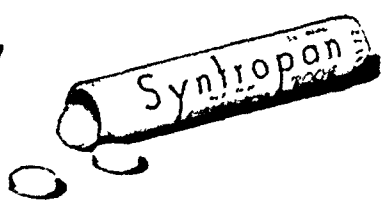
NEW YORK 13, N.Y.

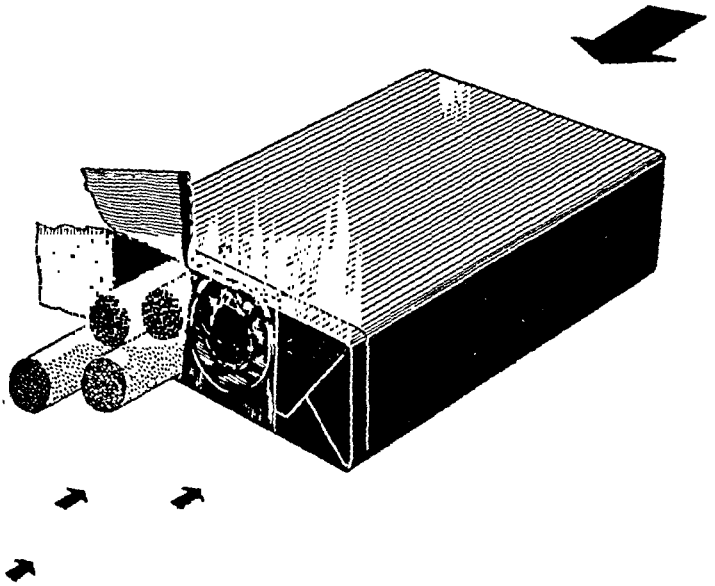
When spasm must be relaxed *Syntropan 'Roche' is a dependable and effective means of restoring normal tone and activity. *INDICATIONS:* Syntropan 'Roche' is indicated in pylorospasm, cardiospasm, intestinal colic, spastic constipation, gastric spasm, spasms due to peptic ulcer, megacolon, and tenesmus. *DOSAGE:* One tablet (50 mg) three or four times a day, or as required. By subcutaneous or intramuscular injection, one ampul t. i. d., or as required. HOFFMANN-LA ROCHE, INC., NUTLEY, NEW JERSEY

*Phosphate of di-tropic acid ester of 3-diethylamino-2, 2-dimethyl 1 propanol.

SYNTROPAN 'ROCHE'

NON-NARCOTIC ANTISPASMODIC





Peace of mind costs even less...

Efficient skin disinfection is priceless and cheap. The Tincture Metaphen required for the average surgical case now costs your hospital no more than a package of cigarettes. Why gamble when you can have so much for so little? The advantages of Tincture Metaphen 1:200 in disinfecting power, relative freedom from irritating effects, and duration of action are a matter of record. In an impartial study* of fifteen antiseptic agents on the oral mucosa, Tincture Metaphen was found to reduce bacterial count 95 to 100% within five minutes; to cause only slight irritation in a few cases, none in others; and to have, in substantial excess over any other antiseptic tested, a two-hour duration of action. Tincture Metaphen may now be obtained by your hospital on more economical terms than ever before.

Abbott Laboratories, North Chicago, Illinois.

*Meyer, E., and Arnold, L. (1938) Amer. J. Digest. Dis., 5:418

Tincture Metaphen

REG. U.S. PAT. OFF.

(4-nitro-anhydro-hydroxy-mercury-orthocresol, Abbott)